



PHD

The syntheses of morphine glycosides

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THE SYNTHESSES OF MORPHINE GLYCOSIDES

Submitted by

Christopher Lacy

for the degree of Ph.D

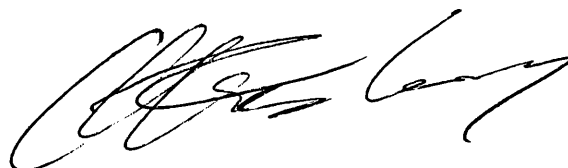
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A handwritten signature in black ink, appearing to read 'Chris Lacy', written in a cursive style.

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To my Mother and Father

ABSTRACT

The morphine metabolite morphine-6-glucuronide is a more effective and longer lasting analgesic drug than morphine with fewer side effects. Unfortunately, morphine is also metabolised to morphine-3-glucuronide, a compound which antagonises the analgesic effect of morphine. Since the 3-glucuronide is formed in greater abundance than the 6-glucuronide, there is much interest in using the latter, rather than morphine, as a pain killing drug.

Syntheses of morphine- and codeine-6-glucuronides have been reported by Yoshimura *et al.*¹¹⁸, but we have been unable to reproduce the methods described and to obtain the products in a pure form. We have significantly improved the coupling procedure by boiling 3-acetylmorphine and methyl bromo-2,3,4-tri-*O*-acetylglucopyranosyl uronate in toluene in the presence of silver carbonate on Celite (1:1), giving the adduct which can be deprotected by treatment of sodium hydroxide and purification by elution through a C-18 cartridge to afford pure morphine-6-glucuronide. Also described are syntheses of the related morphine-6-glucoside, codeine-6-glucuronide, and codeine-6-glucoside using similar methodology.

Other targets are CH₂ isosteres of morphine-6-glucuronide which may provide valuable insight into the nature(s) of the opioid receptors. Although we were unable to complete these syntheses in the time available, some useful investigations were carried out which may provide more focussed direction in future work.

ACKNOWLEDGEMENTS

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I am most grateful to Prof. Malcolm Sainsbury, my supervisor, not only for handing me this project but for his trust, calming influence, and constant source of encouragement and ideas. Special thanks to Prof. Grant Buchanan for providing me with much appreciated help and references in sugar chemistry, and to Dr. Richard Kinsman for his help with the use of C-18 cartridges. I must also thank my industrial supervisors Dr. John Davies and Dr. Mike McPherson for their patience, interest, and helpful discussions.

My appreciation goes to the technical staff at the University of Bath for their invaluable services. Special thanks go to Mr. John Bradley and Mr. Russel Barlow (organic stores), Mr. Dave Wood and Mr. Harry Hartnell (n.m.r. spectroscopy), Mr. Alan Carver (elemental microanalysis), Mr. Chris Cryer (mass spectrometry), Mrs. Jo Curtis, and especially to June and Freda

Finally, I must respect my good friends Matthew Sage, Alan Graham, Simon Diston, Kevin Williams, and Andrew Gaskell for keeping me wild, Sarah Cosway for keeping me tame, and everyone else I worked with, especially Dave Brown, Ali Ninan, Martin Wills, and Matthew Fletcher, for being there when I needed them. Good luck to Maxson Liu with the future work from this project

ABBREVIATIONS

Ac	acetyl
AUC	area under curve
BF ₃ .Et ₂ O	boron trifluoride etherate
β LPT	β lipotropin
Bn	benzyl
Bu	butyl
CNS	central nervous system
conc.	concentrated
CPM	cyclopropyl methyl
CSF	cerebrospinal fluid
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ED ₅₀	effective dose - dosage effective to 50% population
eq	equivalents
Et	ethyl
GIT	gastrointestinal tract
gly	glycine
i.c.v.	intracerebroventricular

ⁱ Pr	isopropyl
i.r.	infrared spectroscopy
LD ₅₀	lethal dose - dosage lethal to 50% population
leu	leucine
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
m-CPBA	meta-chloroperbenzoic acid
Me	methyl
met	methionine
MHP	mouse hot-plate test
m.s.	mass spectroscopy
n-	neo
n-pent	neo-pentyl
n.m.r.	nuclear magnetic resonance
o-	ortho
OPC	organotin phosphate condensate
phe	phenylalanine
Pr	propyl
py	pyridine
R _F	retention factor
s.c.	subcutaneous
TBAF	tetrabutylammonium fluoride
^t BDMS	^t butyldimethylsilyl
^t Bu	tertiary-butyl

Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl (or tetramethylsilane as n.m.r. standard)
TXA ₂	thromboxane-A ₂
UDP	uridine diphosphate
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase

For spectral data:

n.m.r.

s	singlet
d	doublet
t	triplet
q	quartet
pent	pentet
m	multiplet
brd	broad
<i>J</i>	coupling constant (Hz)
Ar	aryl
pyrim	pyrimidyl

i.r.

s	strong
m	medium
w	weak

.

TABLE OF CONTENTS

A.	INTRODUCTION	1
1.	Pain and Analgesia	1
2.	Opioids and their Receptors	6
2.1.	Agonist-Antagonist Behaviour of Opioids	6
2.2.	Endogenous Opioids and Opioid Receptors	7
3.	History of Morphine and Analogues	13
4.	Modifications and Effects of Morphine	16
4.1.	Hydroxyl Groups at C-3 and C-6	16
4.2.	Geometric Modifications	17
4.3.	Nitrogen Substituents	18
5.	Metabolism of Morphine and Analogues	20
6.	Conjugation of Glucuronic Acid	23
6.1.	Glucuronides of Exogenous Compounds	23
6.2.	Types of Glucuronic Acid Conjugation	23
6.3.	Effects	25
7.	Glucuronides of Morphine	26
7.1.	Morphine-6-Glucuronide (M6G)	27
7.2.	Morphine-3-Glucuronide (M3G)	30
8.	Goals	32
8.1.	Current Knowledge on M6G Synthesis	32
8.2.	CH ₂ Isostere Targets	34

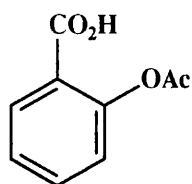
B.	RESULTS AND DISCUSSION	37
1.	Morphine-6-Glucuronide Synthesis	37
1.1.	Attempted Reproduction of Prior Art	37
1.2.	Mitsunobu Reaction	40
1.3.	Attempted Coupling Using Acetyl Activation	42
1.4.	Other Activation Methods	44
1.5.	Coupling Attempts With Benzylated Sugars	45
1.5.1.	Alternative Syntheses of Methyl-2,3,4- tri- <i>O</i> -benzylglucopyranosyl uronate	48
1.5.2.	Attempted Couplings	57
1.6.	Nucleophilic Displacement of Chloride From α -Chlorocodide	59
1.7.	Attempted Glucoside Couplings	61
1.8.	Attempted Koenigs-Knorr Glucosidation	63
1.9.	Attempted Enzymic Coupling	64
1.10.	Couplings Using Silver Carbonate On Celite	65
1.10.1.	Deprotection of Glucopyranoside Products	67
1.10.2.	Glucuronidation Using Silver Carbonate On Celite	68
1.11.	Alternative Claims	73

2.	CH ₂ Isostere Targets	75
2.1.	Attempted Synthesis of Morphine-6-pseudoglucuronide	75
2.1.1.	Pseudosugar Methodology	75
2.1.2.	Synthesis of Epoxide Precursor	77
2.1.3.	Investigation of Coupling Methodology	80
3.	C-Glucuronide Target	84
C.	EXPERIMENTAL	87
D.	REFERENCES	164

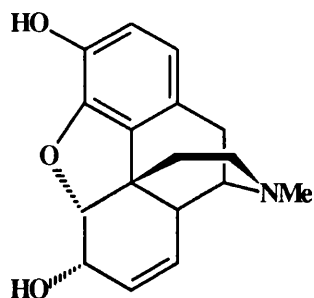
A. INTRODUCTION

1. Pain and Analgesia

Analgesia is an altered behavioural response to pain with diminished ability to perceive pain impulses without loss of consciousness. Pain is the body's defence mechanism, informing the individual of tissue damage during or after its occurrence so that he or she can take evasive action and prevent further damage. However, the mechanism of pain is very complex and the degree of pain is not necessarily proportional to the degree of tissue damage. Often pain exists to a far greater extent than is necessary for its purpose and it is therefore desirable to reduce or abolish its effects. This has been the case since ancient times either with medicines or by more natural means such as meditation. Today, the Western World quite typically prefers the use of medicines and a large area of science is devoted towards discovering new analgesic drugs which are more powerful or less toxic (or both) since the problem is still a vast one. Knowledge of the mechanism of pain is essential if one is to consider the mechanisms of analgesic drug actions. Analgesics acting at peripheral sites such as aspirin **1** are known as anti-inflammatories and this type of analgesia is completely different from the depressant activity in the central nervous system (CNS) effected by narcotic drugs such as morphine **2**.



Aspirin 1



Morphine 2

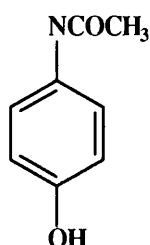
Pain can be separated into two types: 'acute' and 'chronic'.

Acute pain is activated by strong external stimuli, maybe causing or threatening tissue damage, e.g. a burn or a cut. Its simplified mechanism is as follows. Signals (nociceptive impulses) are sent from the point of stimulus, through nerves, mostly to the spine (neural network) and interpreted in the CNS so that site of origin, severity, and type of pain can be established. By passing through the neural network, pain (and other) signals must pass through synapses, whether in peripheral locations or in the CNS. Synapses are very small gaps present at intervals throughout a nerve. The nerve cells (neurons) either side of a synapse are called a presynaptic and a postsynaptic cells. When a pain signal of large enough intensity is transmitted to and excites a presynaptic cell, the cell releases a neurotransmitting substance (excitatory neurotransmitter) which diffuses across the gap (synaptic cleft) and interacts with and excites the postsynaptic cell thus allowing transmission of the pulse to continue.

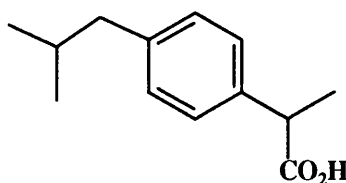
This process may be mediated by the presence of neurotransmitters called presynaptic inhibitors or postsynaptic inhibitors. Presynaptic inhibitors interact with presynaptic cells and block the release of the excitatory neurotransmitter from the presynaptic

terminals. Postsynaptic inhibitors interact with the postsynaptic membrane and decrease the excitability of the postsynaptic neuron¹.

Chronic pain is more difficult to understand and to treat. Its causes are often, in part, psychological, created by depression and anxiety, following surgery or some other cause of intense acute pain. As a result, pain awareness is raised in the CNS so that weak pain signals are subsequently interpreted as a strong pain.



Paracetamol 3

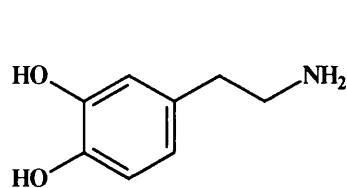
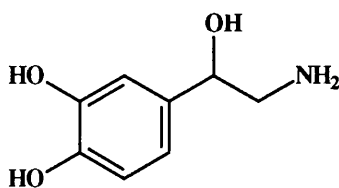
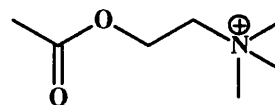


Ibuprofen 4

Pain may be tackled chemically either at the periphery or within the CNS. Blocking at the periphery prevents nociceptive impulses from being transmitted to the CNS. Examples of drugs which act at the periphery include aspirin **1**, paracetamol **3** and ibuprofen **4**, all of which are also anti-inflammatories. In practice, these appear to have both peripheral *and* central analgesic actions although this is not firmly established. Such drugs are known to act by blocking the biosynthesis of prostaglandins and related metabolites which cause pain, fever and inflammation. As indicated above they may also have a role to play in the neural transmission of pain, but direct evidence for this is missing².

Tackling pain at the CNS is the normal way our bodies tackle pain overload. Pain perception and behavioural response to pain is controlled by peptides called

enkephalins (section 2.2.) which are inhibitory neurotransmitters, almost certainly acting by binding with specific receptors in presynaptic cells in the CNS. This prevents the release of pain neurotransmitters in the CNS. These neurotransmitters are dopamine **5**, noradrenalin **6**, acetyl choline **7** or substance P, depending on the exact location and effects.

Dopamine **5**Noradrenalin **6**Acetyl choline **7**

The CNS then reduces the appreciation of pain relative to the level of nociceptive impulses. High levels of enkephalins or low levels of synaptic neurotransmitter may block enkephalin release³⁻⁶. Narcotic analgesics such as morphine and related opioids are centrally acting and mimic the action of enkephalins by binding at the same opioid receptor sites. Awareness of pain may persist but the ability to interpret, integrate and react to pain is decreased with sedation, euphoria, and reduced anxiety and suffering. However, this type of analgesia has its drawbacks. Such euphoria gives the opioids abuse potential and it is known that opium has been used for euphoric purposes for centuries.

In addition, following the euphoria often comes depression (itself producing chronic pain) which is only alleviated by taking more of the drug, resulting in physical dependence. Speculations have been made that since high levels of narcotic analgesic or low levels of synaptic neurotransmitter may block enkephalin release³⁻⁶, this would

result in low levels of enkephalins once the effects of narcotic have worn off. Other side-effects of opioids will be discussed later.

Analgesics which act at the CNS are generally regarded as very potent compared with the peripherally acting anti-inflammatory pain killers and are frequently used to treat both acute and chronic pain. However, due mainly to the dependence liability, opioids are only used to treat acute pain if it is too severe for peripherally active drugs to have an effect. Chronic pain is almost exclusively treated with CNS depressants, the psychological and emotional effects in addition to analgesia of such drugs being ideal in such cases. Anti-inflammatory drugs are generally used for acute pain. For example, labour pains can be treated with an epidural of a peripherally acting pain-killer which repeatedly completely blocks the initiation of pain signals locally, while opiates only partially alleviate such pain making it acceptable.

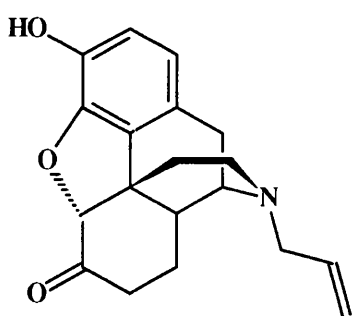
2. Opioids and their Receptors

2.1. Agonist-Antagonist Behaviour of Opioids

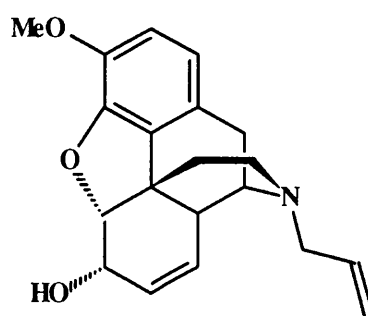
An agonist is a substance which binds to an active site, promoting a pharmacological response.

An antagonist is a substance which competes with an agonist to bind to an active site and inhibit a pharmacological response.

The terms when applied to opioids complicate the issue somewhat. Although morphine inhibits a pharmacological response (pain), the effect of analgesia must also be considered, since this is due to the effect morphine has at the 'so called' opioid receptors (section 2.2.). Thus, morphine acts as an agonist, at some of these sites, at least.



Naloxone 8



Nalorphine 9

Compounds such as naloxone **8** compete with morphine, reversing the analgesic effect and are thus termed opioid antagonists. Naloxone is an example of a pure opioid antagonist because it has no analgesic activity itself. However, compounds exist (e.g.

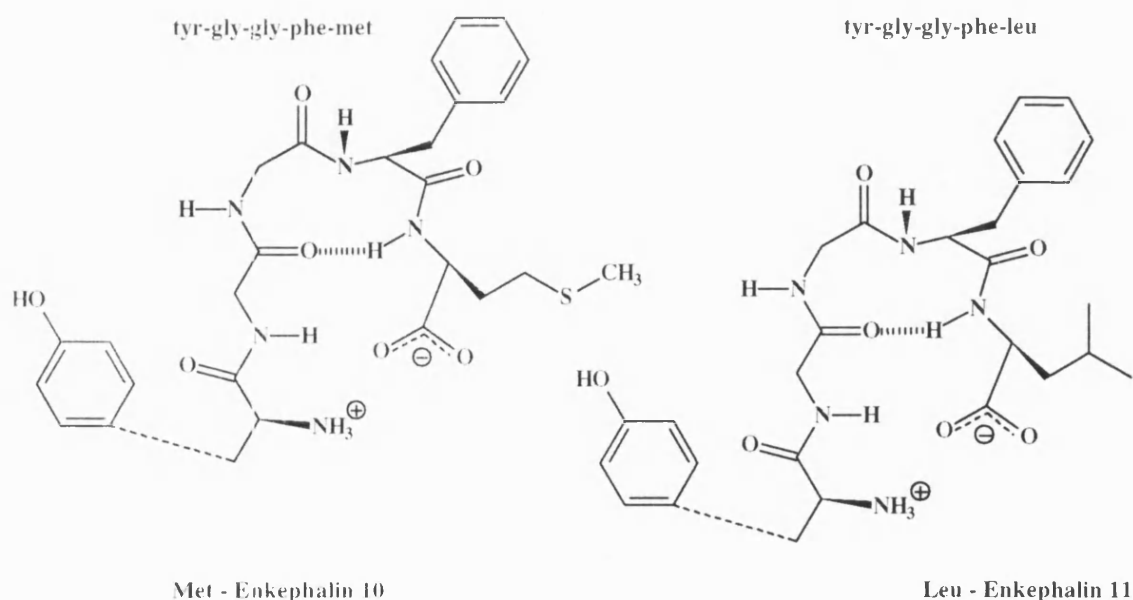
nalorphine 9) which block the action of morphine but also exhibit some analgesic activity. These compounds are termed 'mixed agonist-antagonists' or 'dualists'.

2.2. Endogenous Opioids and Opioid receptors

Opioid receptors were originally conceived as specific sites in the CNS that form a crucial link in the mechanism of pain perception and that fail to function in this respect when bound to certain ligands (analgesics). Before 1970 there was no direct evidence for opioid receptors. Their existence had been inferred from stereochemical structure-activity relationships of narcotic analgesics and their specific antagonists. It was not until the early 1970's that direct evidence of their existence and location came to light thanks to stereospecific binding studies by Goldstein *et al.*⁷, which pioneered work in this area. Following the demonstration of the existence of opioid receptors came the question of their physiological role. It is unlikely that the receptors should have evolved uniquely for reaction with substances exogenous to the body, and it is logical to postulate the existence of natural morphine-like substances that associate with opioid receptors in an interaction that has some physiological function, such as the transmission or modulation of nerve impulses.

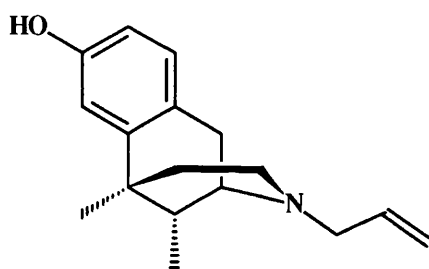
This prediction, first made by Goldstein⁸, stimulated an intensive search for substances of natural occurrence with opioid-like properties. During 1974-5 several groups isolated substances from brain tissue that acted as agonists at opioid receptor sites⁹. Isolation techniques by Hughes *et al.*^{10,11} led to the discovery and isolation of a peptide called enkephalin in pig brain. Later it was deduced that this compound was a mixture

of methionine enkephalin (met-enkephalin **10**) and leucine enkephalin (leu-enkephalin **11**) in the ratio 3-4:1.



The enkephalins share the same sequence of four amino acids (tyr-gly-gly-phe...), but are terminated by methionine or leucine residues, respectively. Their precursors, called dynorphins¹² and endorphins, polypeptide fragments of β -lipotropin (β -LPT, 91 residues), of which β -Endorphin (61-91 residues) is 20-30 times as potent as morphine¹³, have also been elucidated. Endorphins have limited drug use since they are rapidly hydrolysed in tissues, especially in the brain. It is assumed that they adopt conformations which fit opiate receptors. The story does not end here and to date some 20 endogenous opioids are known. These are biosynthesised from pro-opiomelanocortin, pro-enkephalin, and pro-dynorphin at the site where they are required¹⁴⁻¹⁶. These findings and research with synthetic agonists and antagonists provides evidence for multiple receptors. Martin *et al.*^{17,18} postulated the existence of

distinct μ , κ , and σ opiate receptors based on differential behavioural and neurophysiological responses to morphine (μ agonist prototype) and two benzomorphan derivatives, ketocyclazocine **12** (κ agonist prototype) and N-allylnorphenazocine **13** (σ agonist prototype).



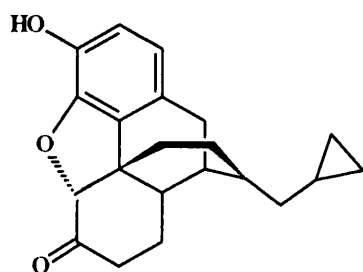
N-allylnorphenazocine 13

Thanks to the discovery of enkephalins, new ligands for pharmacological experiments became available to test opiate receptors and a new receptor-ligand interaction was revealed in mouse *vas deferens*¹⁹. The new receptor was termed δ , its agonist prototype being leu-enkephalin. Similarly a β -endorphin selective 'e' receptor was found in rat *vas deferens*²⁰ and has been suggested to occur in the peripheral nervous system²¹, and another, dynorphin selective receptor (no Greek letter) was found in mouse *vas deferens* by Wuster *et al.*²².

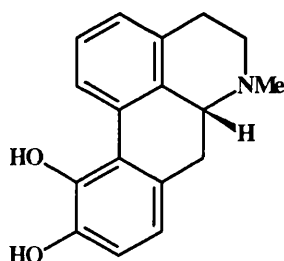
At synapses, neurotransmitting substances are required to pass between the pre- and post-synaptic terminals in order that the signal continues towards the CNS. It is known that μ receptors mediate the release of noradrenalin, κ receptors mediate dopamine and δ receptors mediate acetylcholine²³⁻²⁵. β -Endorphin, generated from proenkephalin, has been shown to interact equally well with central μ and δ binding sites, with very low affinity for κ sites in rat brain membranes²⁶.

μ Receptors are proposed to mediate analgesia, a behavioural pattern (the variability depending on the species) and well defined alterations of vegetative functions (i.e. those which are independent of the brain)^{17,18}.

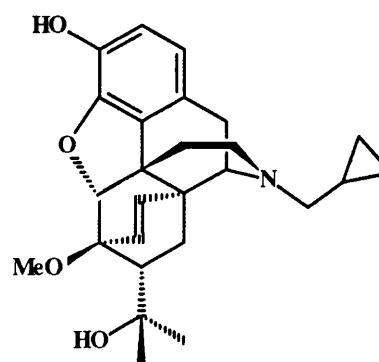
Tolerance to these agonist effects can be developed by chronic administration of morphine-like drugs, and the agonist effects can be readily antagonised by naloxone and naltrexone **14**. The μ receptor appears to be simple in type and is not particularly selective. It prefers relatively rigid ligands, whether they are peptides or morphine surrogates^{27,28}. Two distinct sub-types of μ receptor are now known^{29,30}. The type for which morphine is the prototype ligand is designated μ_2 while μ_1 is a high affinity receptor located in supraspinal regions and found to a large degree in periaqueductal grey. High affinity binding to μ_1 is achieved equally by morphine and leu-enkephalin (which binds to δ , but not to μ_2 receptors).



Naltrexone 14



Apomorphine 15



Diprenorphine 16

μ_2 Receptors appear to mediate respiratory depression rather than analgesia as effected by μ_1 agonists. Certain breeds of mice, which are considered insensitive to opioid antinociception, have a lower composition of μ_1 in periaqueductal grey³⁰.

κ Agonists produce analgesia, but fail to substitute for morphine in suppressing morphine withdrawal symptoms^{17,18}. Naloxone and naltrexone are considerably less effective antagonists against the effects of κ agonists, than they are against those of μ agonists^{17,18,31,32}.

The σ agonist N-allylnorphenazocine has no significant analgesic action in dogs, but precipitates abstinence syndrome in morphine dependent animals due to its affinity for the μ receptors³³. Behaviour in dogs to this drug is quite different from that attained by μ or κ agonists, sharing features with the dopamine receptor stimulant, apomorphine **15**. The behavioural pattern (naltrexone reversible) in dogs is characterised as mania^{17,18} but shares similarities with hallucinogenic effects of certain opiates in other species.

The δ agonist, leu-enkephalin may elicit epileptic seizures following *in vivo* administration^{34,35} to mammals. The high δ selectivity of δ agonists causes the high relative agonist potencies shown by them in mouse *vas deferens* (high δ composition) compared with the guinea-pig ileum^{19,32}. Antagonist potencies of naloxone and naltrexone at these sites are significantly lower than at μ receptors^{32,36,37}. Diprenorphine **16** has been reported to have higher relative antagonist potency than naloxone at δ receptors³⁸. δ receptors accept flexible ligands more readily than rigid ones^{27,28} (c.f. μ) and no cross tolerance is observed between μ and δ receptor prototypes^{39,40}.

The above summary is a very simplified view of opioid receptors. The actual situation is far more complicated with variable effects between species and even the type of administration of test compounds since this affects the localisation of concentration of the test compound. Subtle differences may exist between receptors of a given type

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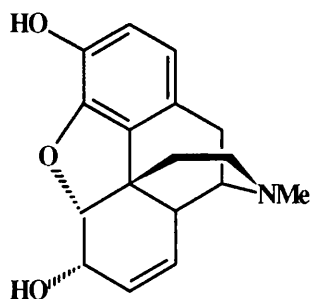
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depending on the cellular environment, especially when considering the binding effects of bulky ligands (such as β -Endorphin). This may give rise to receptor sub-types, e.g. β -endorphin shows >100 times binding affinity to presynaptic μ receptors in rat neocortex (noradrenalin nerve terminals) than presynaptic δ receptors in rat striatum, but shows equal affinity at μ and δ sites in rat brain. Certainly this suggests that there are different μ sub-types⁴¹.

3. History of Morphine and Analogues



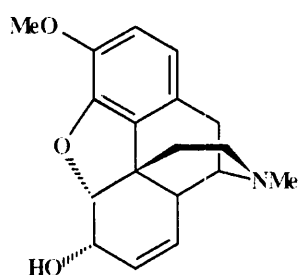
Morphine 2

Figure 1.

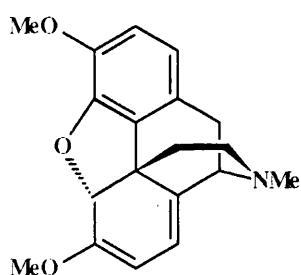
Opium has been used for centuries as a narcotic agent and as a pain killing substance.

In 1805, the German pharmacist Serturner isolated the main active constituent and named it morphine **2** after Morpheus, the God of sleep and dreams. It was not until 1925 that Gulland and Robinson⁴² deduced the correct structure as that in figure 1.

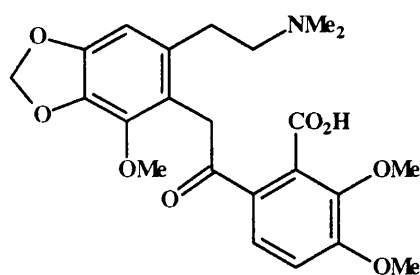
Also isolated from opium in 1832 was codeine **17**, and later, thebaine **18**, narceine **19**, narcotine **20** and papaverine **21**.



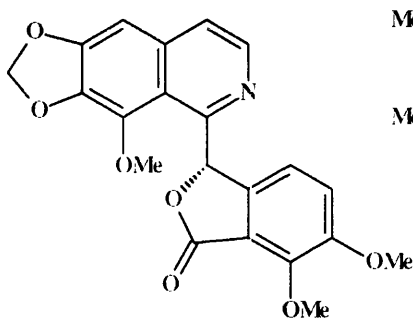
Codeine 17



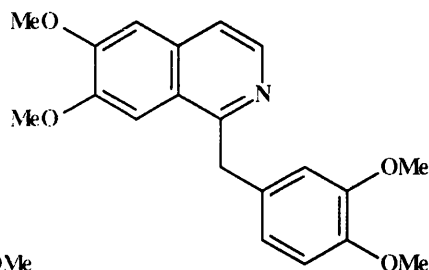
Thebaine 18



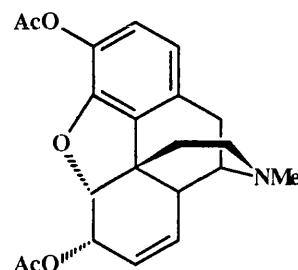
Narceine 19



Narcotine 20



Papaverine 21

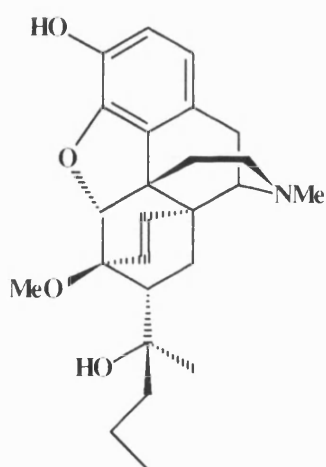


Heroin 22

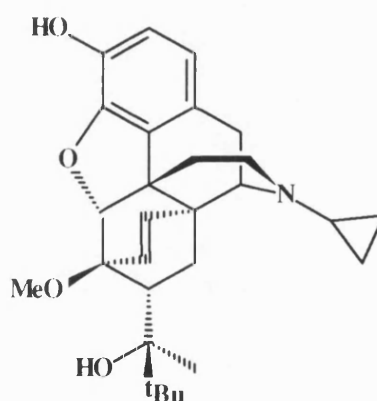
The opposite enantiomer of morphine elicits no opioid pharmacological responses. The effects of morphine are on the CNS and upon the gastro-intestinal tract (GIT). Most important is its ability to suppress pain without the patient losing consciousness, but in addition it induces drowsiness, respiratory depression (fatal overdoses are almost always due to this effect), mood changes leading to physical dependence, reduction in propulsive movements of the intestine (GIT motility) and causes nausea and vomiting⁴³⁻⁴⁹.

Over the past 70 years or so there have been numerous attempts to synthesise analogues to suppress the undesirable actions of morphine whilst maintaining a high level of analgesic activity. One of the earliest was acetylation to diacetylmorphine⁵⁰ (heroin) 22 which was initially claimed to be a non-addictive drug, but actually produces the same effects at approximately 2½ times the potency of morphine. (-)-

Morphine (the natural enantiomer) was first synthesised in the early 1950's by Gates & Tschudi^{51,52}, and subsequently, several syntheses of morphine and analogues have been reported. These studies have led to the discovery of new derivatives showing a range of activities of the opioid nature⁵³. In the 1960's Bentley and co-workers decided that greater complexity and rigidity could be important for greater analgesic activity and selectivity. This conclusion led to the introduction of a class of compounds called oripavines⁵⁴. These are synthesised from thebaine using Diels-Alder chemistry. Of particular mention in this class is the compound etorphine **23** which has a potency greater than 2000 times that of morphine, but with no greater selectivity of action⁵⁵. A related compound buprenorphine **24**, however, does show a lower level of side-effects compared to its analgesic effect and is now used widely⁵⁶.



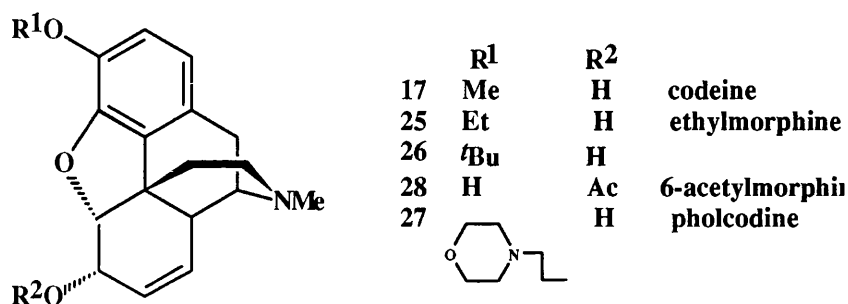
Etorphine 23



Buprenorphine 24

4. Modifications and Effects of Morphine

4.1. Hydroxyl Groups at C-3 and C-6



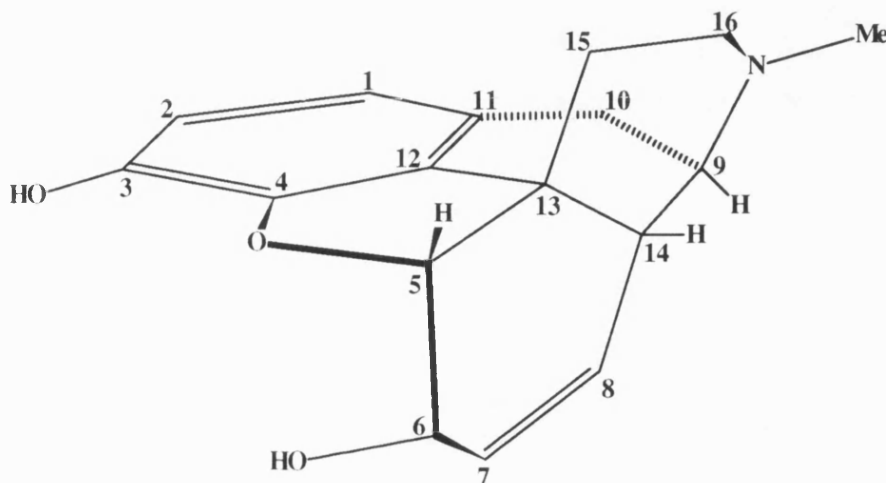
The phenolic 3-hydroxyl group of morphine may augment through hydrogen bonding the binding of the opiate aromatic pharmacophore to its receptor binding site. Masking of the 3-OH group by conversion to the methyl ether **17** (codeine) or ethyl ether **25** (ethylmorphine) groups that are not easily hydrolysed *in vivo* give analgesics with about one tenth the activity of morphine. Although codeine probably exerts an analgesic activity in its own right, the controversial view that it requires prior metabolic conversion to morphine has been expressed⁵⁷. The 3-*t*-butyl ether of morphine **26** has been shown to be stable to metabolism in rats⁵⁸ and although *in vitro* its receptor binding capacity is similar to codeine, it is inactive in rat tail flick test or weakly active in the mouse writhing assay.

3-Morpholinoethylmorphine (pholcodine) **27** has found wide application as a cough suppressant (antitussive agent)⁵⁹.

In contrast to the reduction in activity when the 3-OH is protected, the 6-sulfate ester and 6-glucuronide have been shown to have greater analgesic potency^{60,61}. Heroin has

been shown to be rapidly hydrolysed to 6-acetylmorphine **28** *in vivo* and this accounts for its activity⁶². 6-Acetylmorphine is itself about 4 times as potent as morphine⁶³.

4.2. Geometric Modifications



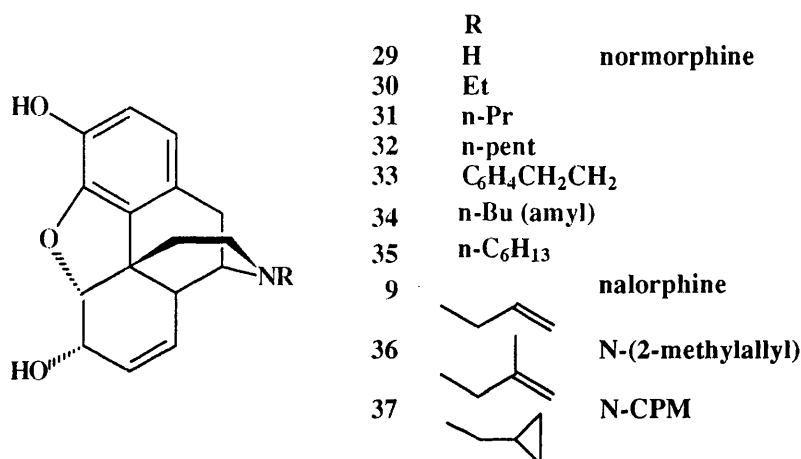
Structural representation of morphine

Figure 2.

The stereochemistry of morphine was finally established unambiguously from an x-ray crystallographic analysis of the hydrocodide dihydrate salt in 1955⁶⁴. In the solid state, the piperidine ring exists in a chair conformation with the NMe group oriented exclusively equatorially. Morphine has 5 asymmetric centres; 5(R), 6(S), 9(R), 13(S) and 14(R). ¹³C Nmr studies suggest that the solution conformation may differ from the solid state form⁶⁵. The simplest geometric change can be studied at C-6. The C-6 epimer of morphine is α -isomorphine, which has antinociceptive actions similar to morphine, but with reduced toxicity while isocodeine is less active than codeine. Stereochemistry at C-14 gives morphine a B/C *cis* ring fusion. Inversion gives B/C *trans* morphine, which has lower antinociceptive activity than morphine^{66,67}. Both

have C-ring boat conformations due to constraint by the 4-5 epoxide bridge. Without the epoxide bridge, morphinans have a chair conformation for the C ring and B/C *trans* morphinans have higher activity than B/C *cis* morphinans. (+)-Morphine, (+)-codeine, and (+)-heroin are all devoid of antinociceptive activity in the mouse hot plate assay⁶⁸.

4.3. Nitrogen Substituents



It was once believed that a tertiary N bearing a relatively small alkyl substituent was necessary for the activity of narcotic analgesics^{69,70}. However, normorphine⁷¹ **29** (N-H) shows higher analgesic activity than morphine when administered to mice. Replacement of N-Me with N-ethyl **30** resulted in only a slight fall in analgesic response while increasing the hydrophobic series with propyl **31**, pentyl **32** and phenylethyl **33** groups give an increase in activity (6 times for the latter)^{72,73}. N-Amyl **34** and N-hexyl **35** have similar activity as N-methyl substituents. N-Allyl codeine is shown to antagonise the sedatory and respiratory depression effects of morphine⁷⁴. N-

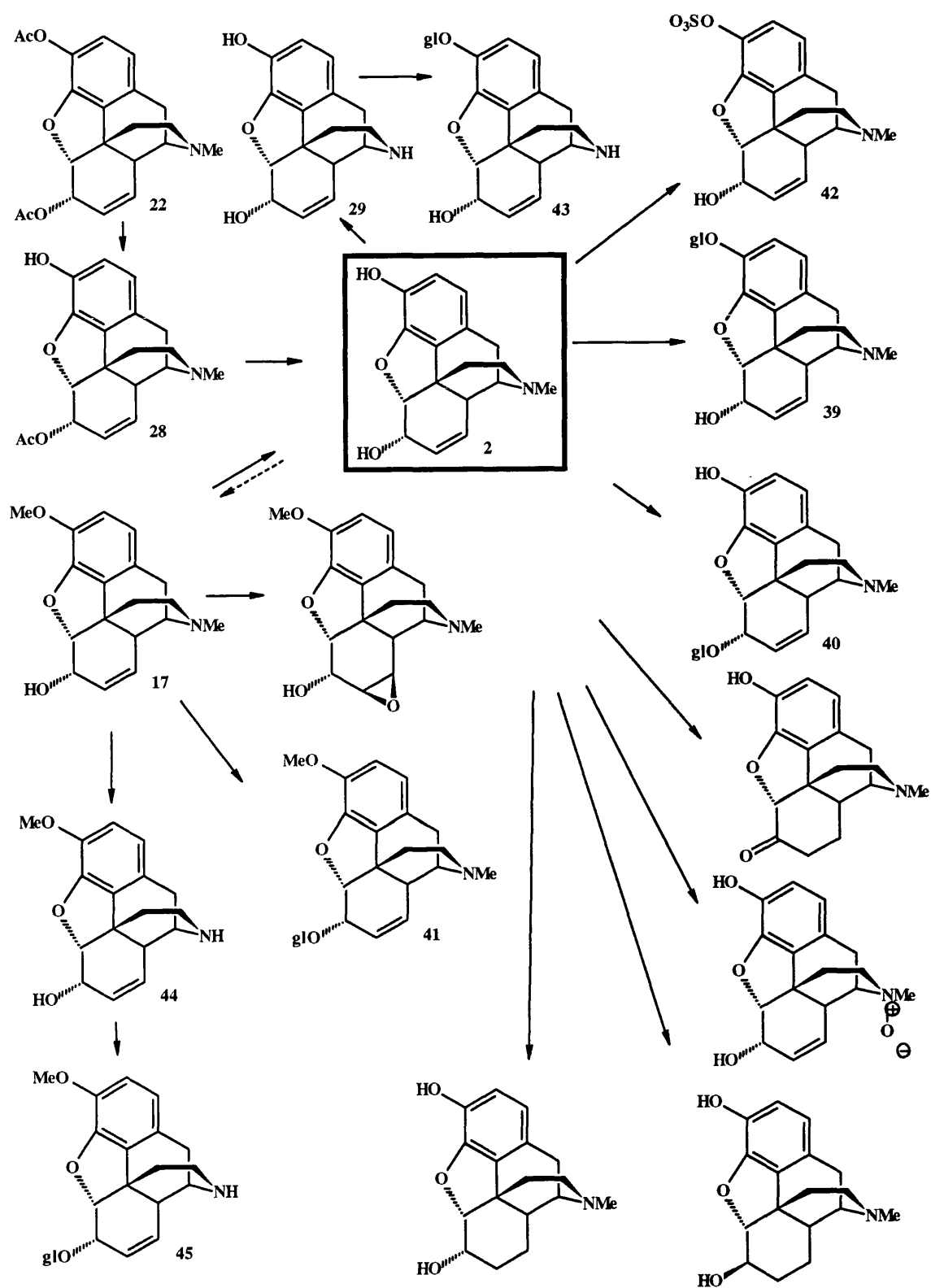
Allyl normorphine (nalorphine **9**) was prepared in 1941 and shows dualist properties. It is an analgesic with low respiratory depression properties, but powerful morphine antagonist activity^{75,76}. N-Propylnormorphine **31** is also a good antagonist⁷². These findings lead to a new area of research into analgesics which possess agonist and antagonist properties without the undesirable effects similar to morphine^{77,78}. Evidence suggests that normorphine is an antagonist at μ receptors and an agonist at either κ or σ receptors⁷⁸. It has roughly equal agonist activity to morphine and reverses actions of morphine on GIT and CNS, reversing respiratory depression, but by itself it gives rise to respiratory depression, anxiety, hallucinations, nausea, difficulty in focusing and insomnia⁷⁹. N-(2-Methylallyl) **36** and N-CPM⁸⁰ **37** analogues are more potent antagonists than nalorphine, the latter by 3 times, but also 3 times more active as an agonist than morphine. It seems that N-substituents with straight chains of 3 carbons gives optimum antagonist activity. Increasing the chain length by one carbon lowers activity, and by two or more carbons restores agonist activity⁷⁹.

5. Metabolism of Morphine and Analogues

The metabolism of morphine is very rapid after parenteral administration but unpredictable after oral dosage. The pathway is summarised in scheme 1⁸¹.

Conjugation with glucuronic acid **38** is the major elimination route that occurs at the 3-OH and to a lesser extent at the 6-OH positions of morphine, giving **39** and **40** respectively, and at the 6-OH position of codeine giving **41**. This route accounts for 65% of morphine in urine of humans⁸³.

Morphine-6-glucuronide **40** has been proposed as an active metabolite of morphine⁸⁴. It is stable *in vivo* and has up to 4 times the analgesic potency of morphine with about twice the duration of activity. It has also been shown to have 45 times morphine's response upon intracerebral injection and stereospecific receptor binding affinity studies demonstrate this metabolite to have higher receptor binding affinity than morphine (see later). Similar results were reported for morphine-6-sulfate⁸⁵. Morphine-3-glucuronide **39** and the corresponding 3-sulfate **42** had no MHP activity and morphine-3-phosphate and morphine-6-phosphate were similar to morphine in their responses. These activities were reflected in increased agonist potencies (3x) exhibited by nalorphine-6-glucuronide and 6-sulfate with a maintenance of antagonist actions⁸⁵.



Scheme 1.

Heroin is rapidly metabolised in humans⁸⁶ and other species to 6-acetylmorphine **28** and to morphine, the active metabolites⁸⁷. Compounds lacking a free 3-OH function bind poorly to opioid receptor preparations and heroin is no exception. Morphine and 6-acetylmorphine bind well to receptor preparations and the binding of the latter accounts for all the apparent binding of heroin. In addition to 6-acetylmorphine and morphine, morphine-3-glucuronide occurs as a major metabolite of heroin and minor quantities of morphine-6-glucuronide and normorphine **29** and its glucuronide **43** have also been detected in human urine after heroin administration⁸⁸.

N-Demethylation is a significant metabolic route in animals leading to normorphine from morphine and to norcodeine **44** from codeine. These metabolites may in turn be eliminated as their 3 and 6-glucuronides, **43** and **45** respectively. Oxidative removal of an N-methyl function appears to be only a minor metabolic process in humans and is unlikely to contribute to the analgesic effects of morphine to any extent⁷¹.

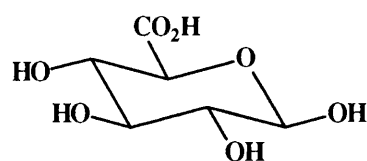
6. Conjugation of Glucuronic Acid⁸⁹

6.1. Glucuronides of Exogenous Compounds

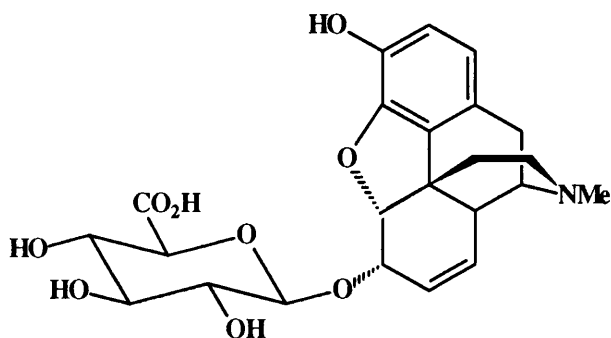
The majority of foreign compounds undergo metabolic transformations in the animal body and these play an important role in any therapeutic action or toxicity displayed by such compounds. Compounds may undergo oxidations, reductions, or hydrolyses but usually (frequently following such transformations) a conjugation reaction occurs during metabolism. The main conjugation reactions which occur in laboratory animals are those involving glucuronic acid **38**, sulfate, glycine, cysteine, methylation and acetylation. Of these, glucuronic acid conjugation is probably the most important for it occurs extensively in man and all laboratory animals except the cat. Conjugations are generally regarded as detoxification mechanisms since the products are usually less toxic and more rapidly excreted than their precursors.

6.2. Types of Glucuronic Acid Conjugation

Glucuronic acid conjugation can occur with several types of hydroxyl, amino and carboxyl groups and with sulfhydryl groups. If a drug contains one of these groups then conjugation can occur directly.



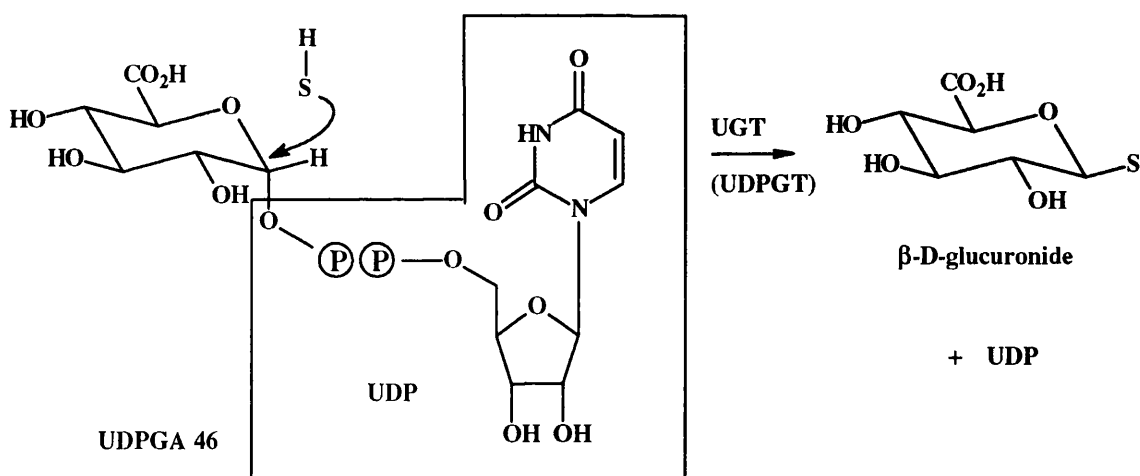
Glucuronic acid 38



Morphine-6-glucuronide 40

If it does not contain such a group or the group is unreactive to conjugation (due to steric hindrance for example), it may acquire one by a metabolic reaction (oxidation, reduction or hydrolysis). Examples of drugs capable of forming the glucuronide directly are widespread, but include morphine **2** and paracetamol **3** thanks to their hydroxyl functions.

The biosyntheses of these glucuronides can be summarised by the mechanism shown:



Scheme 2.

The drug couples in one step to uridine diphosphate-(UDP)-glucuronic acid **46** using one of the enzymes in the family of UDP glucuronosyl transferases (UGT's). The

highest activity of UGT's is found in the liver but several other organs contain them. Detoxification can occur in the skin, lung, kidney, and small-intestine, which is useful since they are directly exposed to xenobiotics or toxins. Evidence suggests that UGT's exist in multiple forms in most species. Eight hepatic UGT's have been isolated in humans.

6.3. Effects

The effect of conjugation of a drug with glucuronic acid **38** is to produce a strongly acidic compound, which is more water soluble at physiological pH than the precursor - most glucuronides showing pKa values between 3 and 4. Morphine glucuronides have low pKa values (3-glucuronide = 2.83, 6-glucuronide = 3.23). The pharmacological activities of virtually all glucuronides show no or much less activity than their precursors. There have been a few exceptions to this reported over the last 15 years, the most well documented of these being morphine glucuronides.

7. Glucuronides of Morphine

Morphine is conjugated in a stereospecific manner to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in the liver⁹⁰. Rane *et al.*⁹¹ suggested that in addition to the known 'morphine-UGT', another UGT isoenzyme is present in rat liver since (-)-morphine is metabolised to (-)-M3G only, while (+)-morphine is converted to both (+)-M3G and (+)-M6G in the ratio 1:3 respectively. Prior treatment with phenylbarbitone (which induces morphine-UGT) increases this ratio to 1:7.4 suggesting that morphine-UGT is not involved with formation of (+)-M3G. Coughtrie *et al.*⁹² confirmed the existence, in rats, of two UGT isoenzymes both involved with regio- and enantioselective glucuronidation of morphine and speculated that morphine-UGT is involved in (-)-M3G and (+)-M6G formations while the UGT involved with (+)-M3G was consistent with bilirubin-UGT but may be a previously undescribed type. In humans, they discovered that the kidney metabolised both (+)- and (-)-morphine almost exclusively to the 3-glucuronide which suggested absence of at least one UGT isoenzyme responsible for (+)-M6G and probably (-)-M6G. The liver gave different results with (+)-morphine metabolised to (+)- M6G and (+)-M3G in the ratio 3.72:1 and (-)-morphine to (-)-M6G and (-)-M3G in the ratio 0.16:1. These results were mean values from such a varying range of results that the standard deviation was >100%. The cause for this could not be confirmed but could be due to variation in time after death of organs used, drug use or environmental factors, or a combination of these. Other obvious factors such as age and sex did not show any correlation. From other physiological studies they confirmed the existence of at least two UGT's, one for M3G and one for M6G (absent in kidney) which again could be bilirubin-UGT.

It was later shown that differential inhibition of these UGT's *in vitro* was effected by metal ions in guinea-pig liver in the conversion of (-)-morphine to its glucuronides. Cu^+ , Cu^{2+} , and Cd^{2+} were able to inhibit the production of M3G with less effect on M6G production⁹³.

7.1. Morphine-6-Glucuronide (M6G)

There have been several reports since 1970 which show M6G to have high activity. In 1971, Shimomura *et al.*⁶⁰ observed that M6G had direct analgesic effects in the hot plate assay and their subsequent research showed that both M3G and M6G can penetrate the blood brain barrier in rats⁹⁴. They speculated that the inactivity of M3G compared with M6G must be due to differences in receptor binding. However, it took more than a decade for the potential clinical importance of these metabolites in the analgesic actions of morphine to be appreciated further.

A wealth of reports have been published illustrating the increased analgesic activity displayed by M6G versus morphine. A rat tail flick (heat) test showed that M6G was 20 fold more potent than morphine after direct microinjection into the periaqueductal grey while M3G was inactive⁹⁵. Another test showed that after peripheral administration to rats, M6G had twice the analgesic effect of morphine but incredibly, after intrathecal administration, M6G was 650 times more potent than morphine⁹⁶. Hanks *et al.*⁹⁷ recognised reports that, in humans, single oral doses are 6-8 times less potent than direct morphine injections, but after long-term treatment with orally administered morphine, its effects were only 2-3 times less potent than by injection. They found that after a single oral dose, the main metabolite was M3G with very small

amounts of M6G, but after long term treatment, the average ratio of M6G to morphine concentrations was 4:1 in plasma.

By assembling these facts one may speculate that the increased analgesic activity of chronic morphine treatment may be due to a build-up of M6G. Paul *et al.*⁹⁶ gave subcutaneous (s.c.) injections of morphine and M6G to mice. They observed that M6G had a longer onset but higher peak analgesia with much longer duration. Frances *et al.*⁹⁸ gave s.c. and intracerebroventricular (i.c.v.) injections of morphine and its 6-glucuronide into mice. They also found that following s.c. injection, M6G was slightly more effective than morphine at peak levels but lasted 10 times longer. If the analgesic potency was measured by integrating the analgesia/time curve (AUC), M6G was 11 times more active. Following i.c.v. injection, however, interestingly M6G was 48 times more active than morphine at peak activity in the acetic acid-writhing test but an astonishingly 360 times more efficient than morphine in the tail flick test. Both compounds were more effective in preventing writhing but since the M6G:morphine potency ratio is greater in the thermal test (7-8 times) variability in receptor selectivity and/or distribution of concentration is apparent.

As for human tests, two detailed tests on cancer patients have been carried out. In 1991, M6G was tested on its effects on respiratory depression, the most important factor limiting opioid use⁹⁹. It was found that M6G effected less respiratory depression at its analgesic dose than morphine at its analgesic dose or put simply, LD₅₀/ED₅₀ ratio was 3 times higher for M6G than morphine¹⁰⁰. In 1992, Osborne *et al.* published a detailed paper on the analgesic activity of M6G in 20 human cancer patients¹⁰¹. Variability was such that no correlation could be made between dosage and levels or duration of pain relief. The mean half life was calculated as 3.2 h but the

range was 1-7.1 h ! This was probably due to variations in renal function (see below). Most impressive, though, was the absence of morphine's side effects, even at the top dose of 4mg / 70kg. None of the patients experienced euphoria, sedation, respiratory depression, nausea or vomiting. Intravenous administration was well tolerated at all dose levels. Heavyness and mild aching in limbs during and for 5 minutes after administration was experienced by patients at 2 and 4mg / 70kg doses but this is consistent with morphine administration.

A better understanding of these effects can be obtained after studying receptor binding affinities. In 1992, an *in vitro* binding study showed that M6G occupied 10 times fewer opioid sites than morphine for the same writhing analgesia and 50 times fewer sites for equal tail flick analgesia showing that M6G has a higher intrinsic efficacy than morphine⁹⁸. Cross tolerance between M6G and morphine suggests that the same binding sites are involved¹⁰². The variability in effects is due to a variation in binding affinities at the different receptors. The use of specific agonists and, more importantly, antagonists has shown that respiratory depression and GIT motility is mediated through μ_2 (spinal) sites rather than μ_1 (supraspinal) or δ sites^{103,104}. Also, thermal analgesia at the spinal level is mediated mainly through δ receptors⁹⁸. It has been found that M6G shows a 4 fold lower affinity for μ_1 than morphine, slightly lower μ_2 affinity than morphine (both much lower than μ_1), higher δ affinity than morphine and a very low κ affinity (lower than morphine)⁹⁵. The fact that M6G has lower binding affinity to μ receptors but higher antinociceptive potency than morphine disproves the relationship between μ affinity and analgesia. With respect to thermal pain, μ/κ selectivity may be a better indication since κ selective agonists fail to block thermal pain^{98,105-107}. Both μ and κ sites are involved with suppressing writhing in mice¹⁰⁵⁻¹⁰⁷.

All this information which has now been obtained explains many findings in earlier papers when the importance of M6G was not as fully understood. In 1982, Svensson *et al.*¹⁰⁸ discovered that morphine glucuronides accumulate in blood, with chronic dosing of morphine, to levels greater than those of morphine. In 1984, research on patients following kidney transplants implicated the kidney as the major organ of morphine metabolism in humans¹⁰⁹ and Joel *et al.* stressed the importance of intact kidney (renal) function in morphine elimination¹¹⁰.

There now exists a large body of evidence to suggest that patients with impaired renal function are particularly sensitive to morphine because of unusually high levels of M6G in plasma^{101,110-113}. It has been suggested that this is due to diminished elimination of the glucuronides rather than an alteration in the biotransformation of morphine⁹⁵. The lingering M6G can then be reabsorbed into plasma thus maintaining its relatively high concentration over longer periods. Several papers support the above findings. In 1992, it was demonstrated that patients receiving long-term epidural morphine treatment had expected high levels of glucuronides associated with long-term treatment with much higher concentrations of 3-glucuronide but the concentration of M6G peaked in 1h and remained higher than that of morphine which peaked in well under 1h and declined fairly sharply¹¹⁴.

7.2. Morphine-3-Glucuronide (M3G)

As mentioned earlier, it was reported in the early 1970's that both M6G and M3G can penetrate the blood-brain barrier in rats but M3G seems to show no analgesic activity, in contrast to M6G. However, in 1990, Smith *et al.*¹¹⁵ reported that M3G is a potent

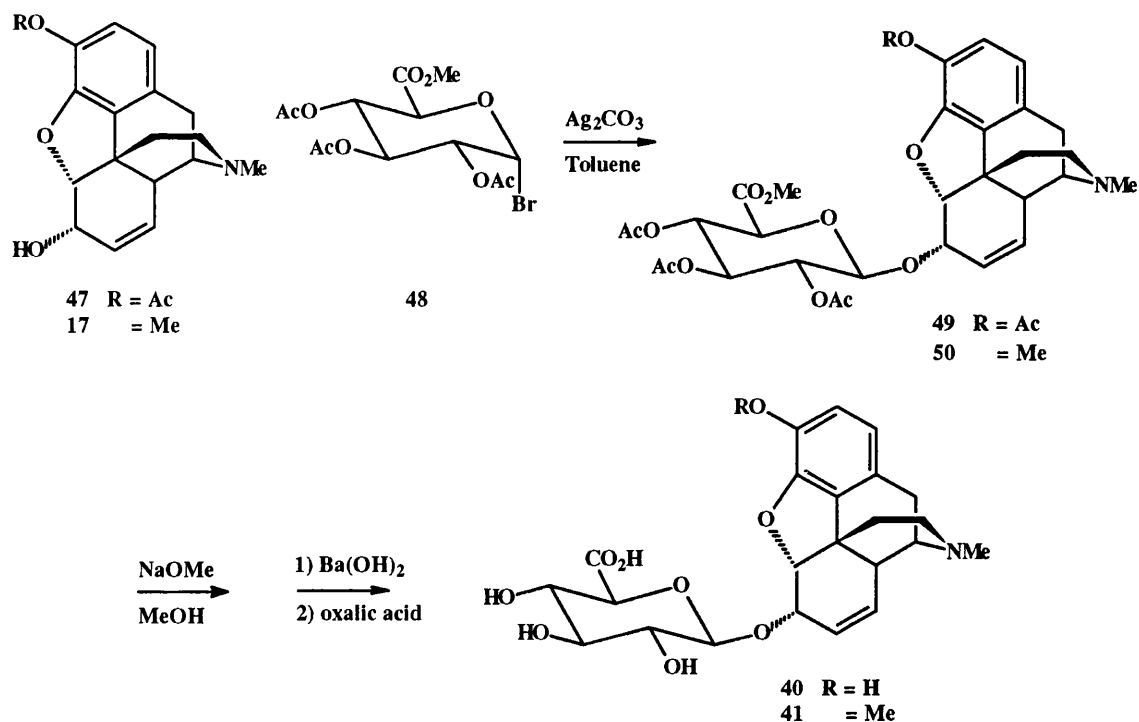
antagonist of morphine and M6G analgesia in rats and, in 1992, this was confirmed when it was shown that M3G antagonised M6G analgesia in hot-plate, tail flick, and writhing assays of rats especially after intrathecal administration¹¹⁶. Also, central respiratory depression was reversed. Since the rat liver converts morphine to 55% M3G and 15% M6G, the concentration of M3G in CSF is high enough after chronic oral doses to have a large effect on the overall analgesic effect¹¹⁶. Contradictory to this, however, was a report on the failure of M3G to antagonise spinal antinociception by morphine or M6G in rats¹¹⁷.

8. Goals

The synthesis and subsequent administration of morphine-6-glucuronide would now seem to be enormously beneficial. Not only is the ratio of desired effects to unwanted effects greater but the higher and longer duration of activity of M6G may result in greater efficiency of morphine per se if a simple procedure for 6-glucuronidation is available. Furthermore, administration of M6G would by-pass the *in vivo* production of M3G which may have antagonist potential in humans, based on findings in rats. In any case, the production in high yields of M6G would be beneficial for further tests on the overall effects of this extremely active and useful metabolite.

8.1. Current Knowledge on M6G Synthesis

The syntheses of morphine- and codeine- 6-glucuronides **40** and **41** have been reported in fair yields (~30%, and ~20%) from 3-acetylmorphine **47** and codeine **17** respectively by Yoshimura *et al.*¹¹⁸.



Scheme 3.

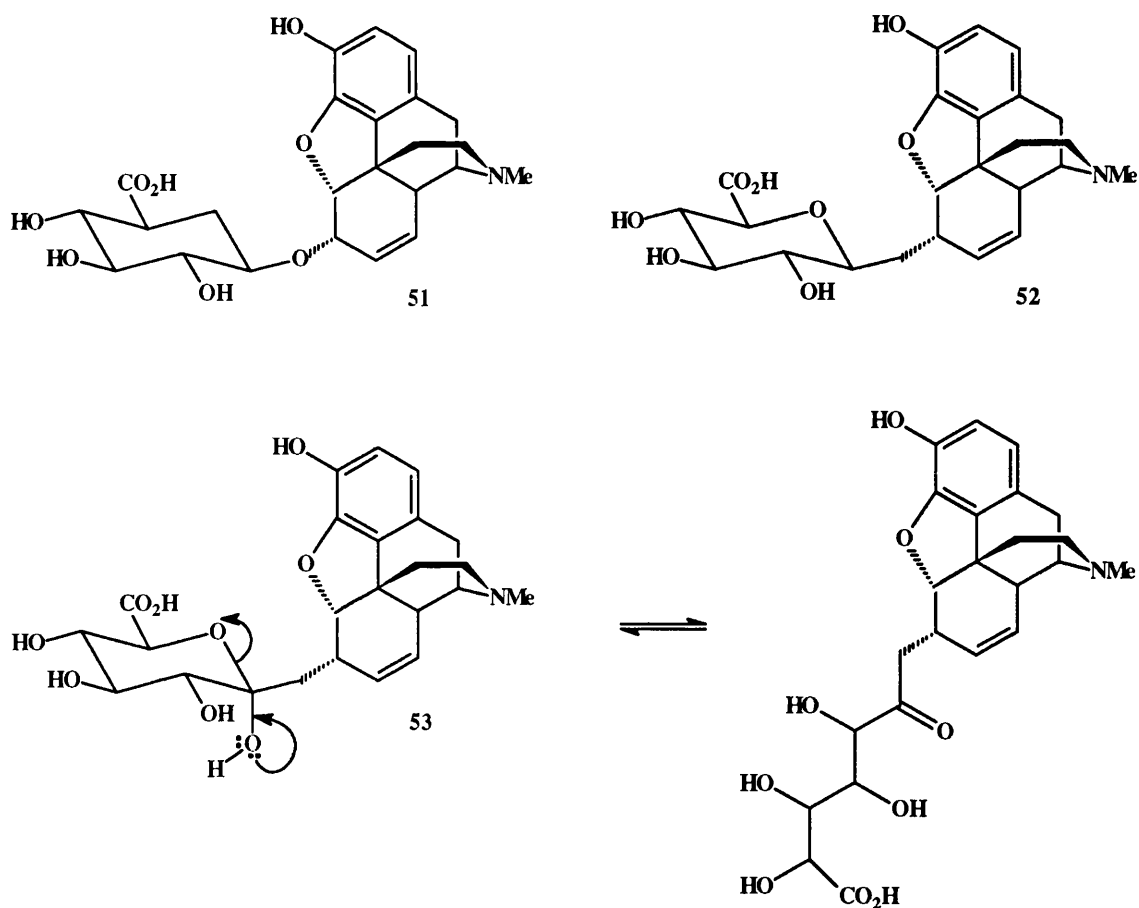
Several groups who performed the pharmacological tests cited above used this procedure without reporting yields, or obtained the metabolite from an outside source. It is common knowledge from the various manufacturers of this metabolite that this procedure gives much lower yields than reported, is difficult to perform and the product is frequently contaminated with metal salts. Macfarlan-Smith, who funded our work, actually failed to produce any of the desired product via this route, hence their interest in finding an alternative synthesis.

8.2. CH₂ Isostere Targets

It was reported in 1991 that both M6G and to a lesser extent M3G display lipophilicity measurements almost as high as morphine itself over a wide pH range¹¹⁹. This does not correlate with the predicted values or with the values for most other glucuronides and an attempt was made to explain the reasons for this unexpected high lipophilicity using theoretical conformational studies. A conclusion was arrived at proposing that the two glucuronides exist in conformational equilibria between extended and folded forms. The extended conformers efficiently expose their polar groups, thus predominating in polar media such as water, whereas the folded conformers mask part of their polar groups, thus being more lipophilic and more likely to predominate in less polar media such as biological membranes. This would explain how these metabolites, especially M6G, have a greater ability to cross the blood-brain barrier than expected.

Not discussed in this report, however, is the possibility that the glucuronides may exist in an equilibrium between closed-ring and open-chain forms in which the latter may have more freedom to expose or mask its polar groups to a greater extent than the former proposed above. Alternatively, it is possible that an open-chain form is simply more polar and it is this equilibrium which gives these metabolites the variability in polarity and lipophilicity which allows a high level of blood transport with the ability to pass into biological membranes.

This gave us the idea of preparing CH₂ isostere targets of the types shown below.



The first two targets **51** and **52** should be unable to exist in open-chain forms and may only equilibrate between extended and folded forms of the type mentioned by Testa *et al.*¹¹⁹. Should these targets show poor biological and physical results, the third target **53** may exist in an open-chain form and a different set of results would be interesting.

In addition to giving more insight into the conformational chemistry of M6G, some of these targets may be expected to show biological activities more or less M6G-like than morphine, thus giving a greater insight into the opioid receptor variables about which, still, relatively little is known. Even if these targets should give poor biological results, a successful synthetic method will open the door to research into a wide range of analogues which may provide vital clues into opioid receptor multiplicity and effects.

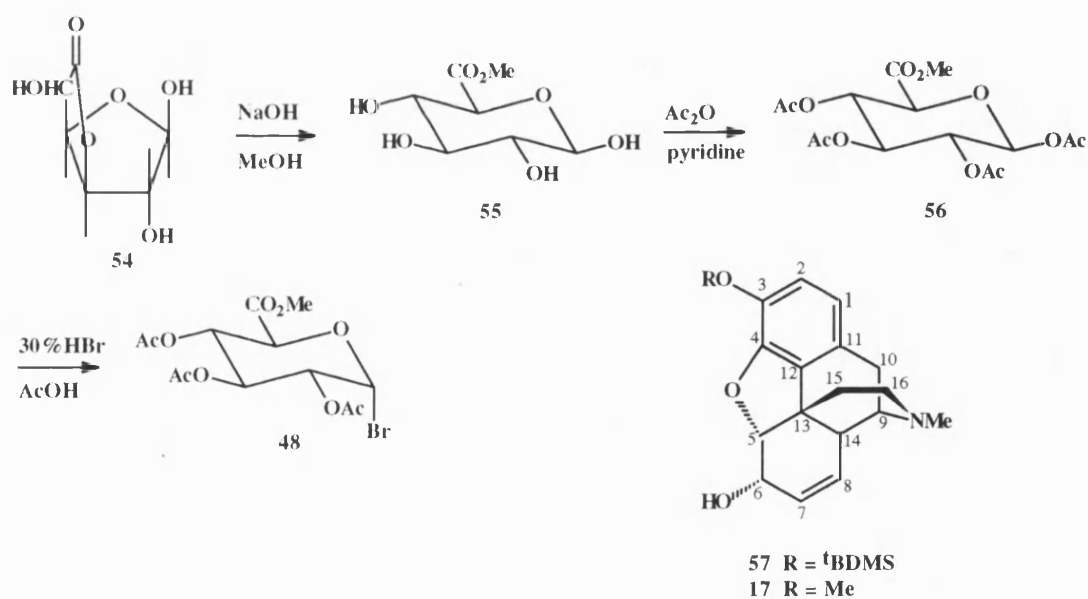
This is more justifiable when considering the more favourable clinical effects of M6G compared with morphine.

B. RESULTS AND DISCUSSION

1 MORPHINE-6-GLUCURONIDE SYNTHESIS

1.1 Attempted Reproduction of Prior Art.

Following the problems encountered by our colleagues at Macfarlan Smith to reproduce the coupling reactions reported by Yoshimura *et al.*¹¹⁸ (scheme 3. Chapter A.), this method was investigated first.



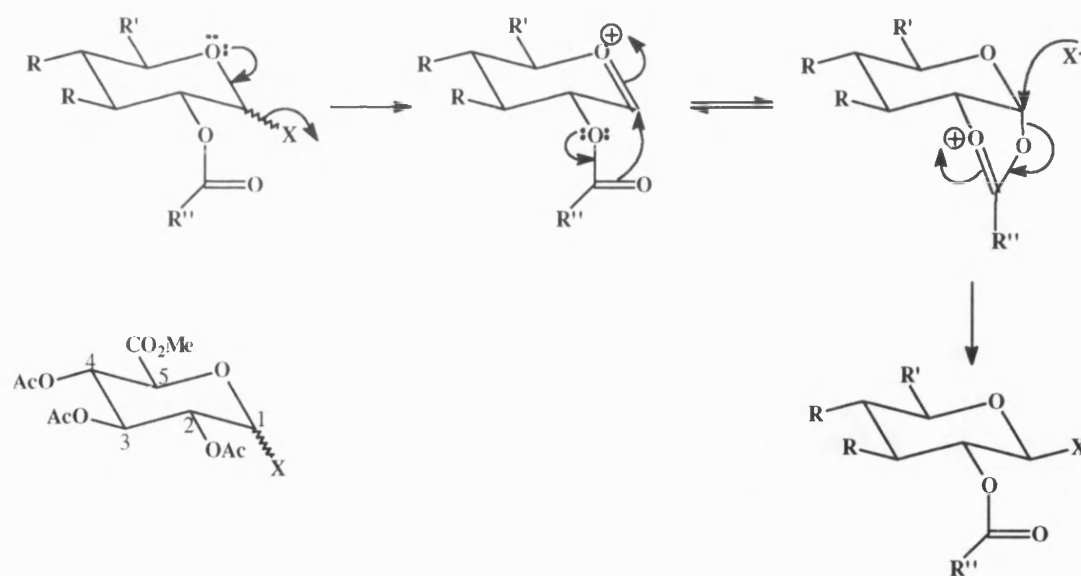
Scheme 4.

Synthesis of the glucuronate precursor, methyl (bromo-2,3,4-tri-*O*-acetylglucopyranosyl) uronate **48**, was successfully achieved from glucurono-6,3-

lactone **54** via methyl glucopyranosyl uronate **55** and methyl tetra-*O*-acetyl glucopyranosyl uronate **56**, as previously described^{120,121}. Two attempts, one to couple 3-*t*-butyldimethylsilylmorphine **57**, and one to couple codeine **17** to the glucuronate **48** were attempted using freshly prepared, oven-dried silver carbonate¹²². In both cases no new products were formed after 20 hours at reflux and starting materials (opioid and glucuronate) were recovered. It is known that the glucuronate **48** is unstable but this does not explain the total lack of reaction. The fact that **48** was recovered suggests that this compound is insufficiently reactive, even with the activating reagent silver carbonate present in excess.

Consequently, an alternative route was sought. An extensive literature search resulted in the discovery of a multitude of possibilities when applied to glucoside couplings, but few in the area of glucuronides.

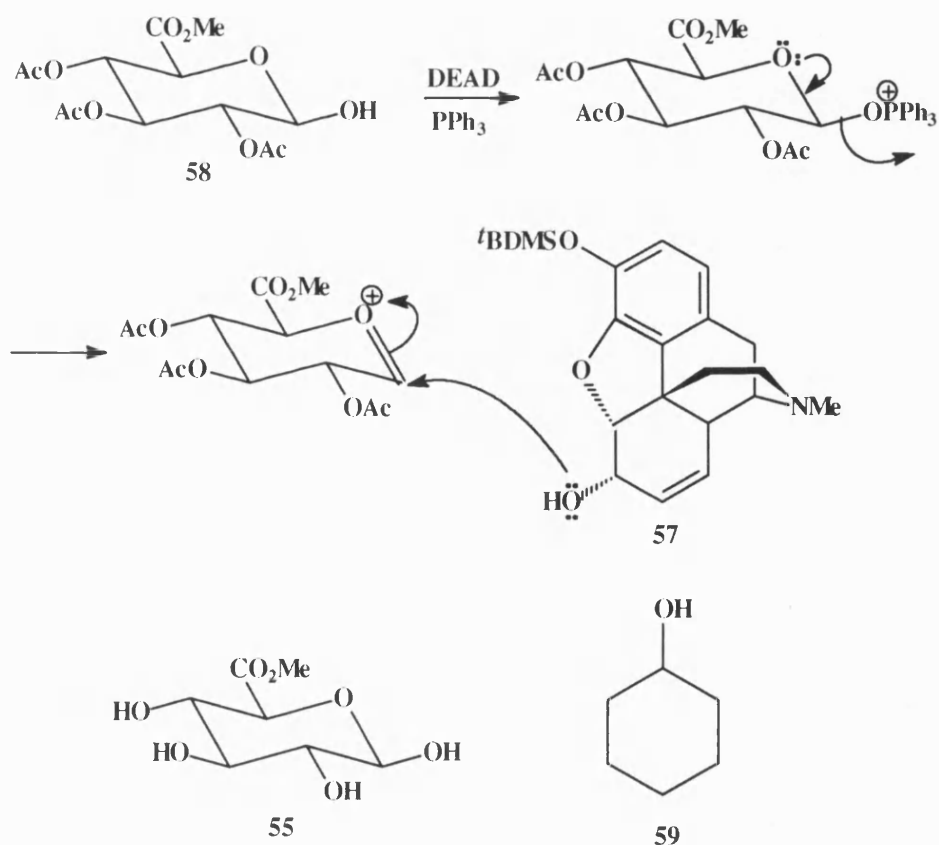
Following a similar line to that used by Yoshimura, we decided that the glucuronate precursor should have the carboxylate group protected as a methyl ester, which is stable to basic and moderately acidic conditions, and to have the non-anomeric hydroxyls (2, 3, and 4) protected as acetate groups. One important feature is that an acyl group at C-2 would control the facial selectivity of the coupling process and give the desired *anti* stereochemistry as a result of the neighbouring group effect¹²³.



Thus, in the case of a glucuronate derivative, the presence of an acyl group at C-2 should result in β -glucuronide formation.

1.2 Mitsunobu Reaction

First attempts by us were based on the Mitsunobu reaction¹²⁴ (c.f. TXA₂ synthesis¹²⁵). This has been used in glycosyl couplings before¹²⁶ and, despite the above stereochemical rationalisation, we first tried to couple the *O*-silylmorphine **57** and methyl glucopyranosyl uronate **55** in tetrahydrofuran (THF) with 1.2 eq diethylazodicarboxylate (DEAD) and 1.5 eq triphenylphosphine, hoping that the lack of protection would not present a problem, but would have the maximum efficiency giving the simplest route to the target compound.



In the event, however, only starting materials and triphenylphosphine-DEAD complex were recovered, indicating that none of the hydroxyl groups on the glucuronate **55** were sufficiently reactive to form the alkoxyphosphonium salt. Since carbohydrates with no hydroxyl protecting groups present tend to equilibrate between open chain and 5 and 6 membered ring forms, it was decided that only suitably protected glucuronate precursors should be used in future. However, an attempted coupling with methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** and silyl-morphine **57** failed, as did a similar reaction using mercuric bromide (1.2 eq) as a promoter¹²⁶.

With consideration to the wastage of the expensive and scheduled substance morphine, the following coupling methodologies were investigated using cyclohexanol **59** as a cheap model and the glucuronate **58** as the glycon.

Once again, the Mitsunobu method failed, with or without mercuric bromide present, and similar attempts were tried with tributylphosphine in place of triphenylphosphine. It is considered that this reagent gives a DEAD complex which is more reactive towards hydroxyl groups and it affords a more reactive alkoxyphosphonium salt.¹²⁷ Unfortunately, the reaction failed, although the hydrazine formed by the reduction of DEAD was isolated. During the reaction, on addition of cyclohexanol at -78°C, the solution immediately turned red, indicating a reaction between the tributylphosphine-DEAD complex and cyclohexanol rather than with the glucuronate as desired. We assume that in this case, dehydration of cyclohexanol occurred, accounting for the formation of the hydrazine. However, when the reaction was repeated with mercuric bromide present, DEAD remained unchanged.

The former of these two reactions was repeated using acetonitrile as solvent since this is said to promote the reaction by stabilising the intermediate oxonium species as a complex¹²⁸ (figure 3).

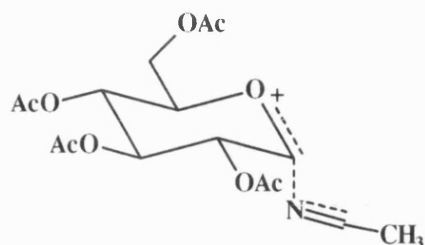


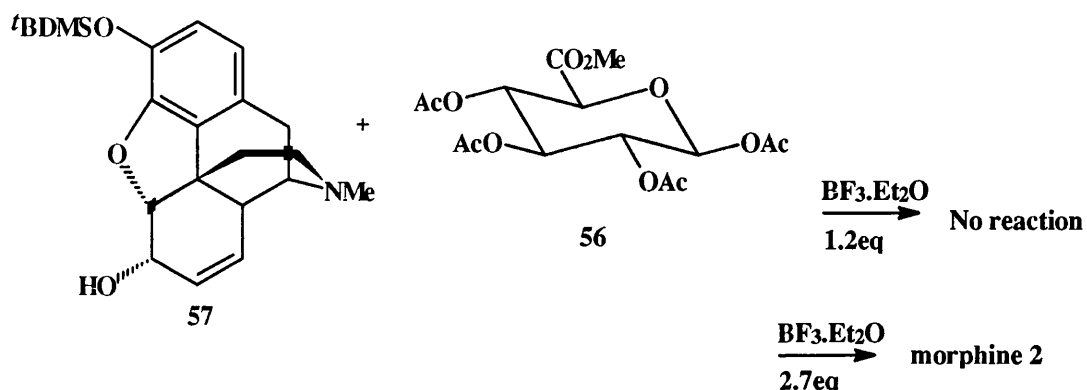
Figure 3.

Indeed the red colouration appeared when the solution was warmed to 0°C, prior to addition of cyclohexanol, and the hydrazine reduction product from DEAD was again obtained. No coupling products were recovered, however, indicating a lack of reactivity between the alkoxyphosphonium salt of the glucuronate precursor **58** and cyclohexanol **59**.

1.3 Attempted Coupling Using Acetyl Activation

The Mitsunobu methodology was abandoned so that other techniques could be investigated. Virtually all glycosyl ether linkages utilise excellent leaving groups at the anomeric carbon. These may be stable groups which are activated *in situ* by a Lewis acid. The majority of such methods are carried out upon glycons with non-acyl protecting groups. However, there is one glucuronidation method which takes place

between a thiol and methyl tetra-*O*-acetyl glucopyranosyl uronate **56** activated with the Lewis acid, boron trifluoride etherate¹²⁹.

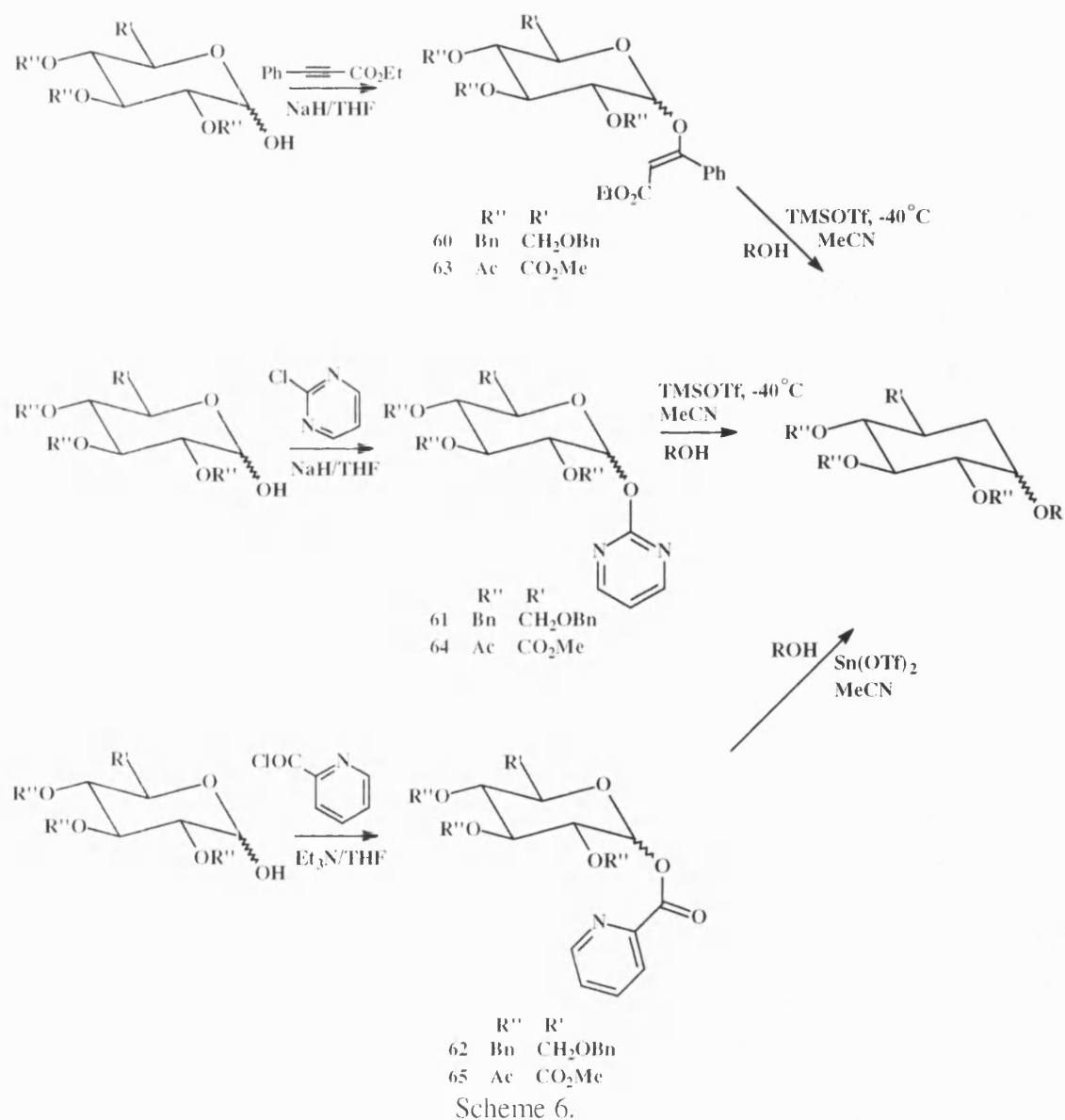


Scheme 5.

In principle, thiols are softer and more nucleophilic than alcohols, but we were still motivated to investigate this methodology using our silylmorphine derivative **57**. The first attempt was carried out using 1.2 eq boron trifluoride etherate, but this failed and it seems likely that most of the reagent was used up by binding to the basic nitrogen atom of the silyl-morphine **57**. To overcome this, the reaction was repeated using 2.7eq boron trifluoride etherate to give sufficient excess to activate the glucuronate **56**. The only result, however, was the desilylation of **57** to give morphine **2**.

1.4 Other Activation Methods

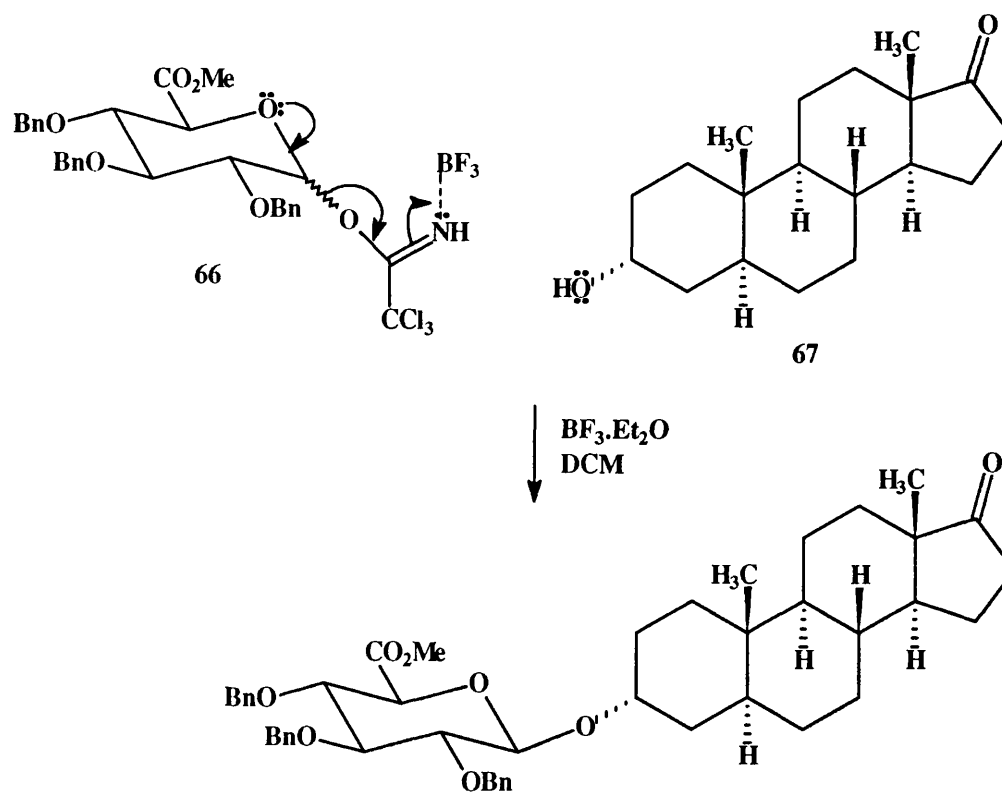
We next investigated three glucosidation methods which have been used to couple the benzyl derivatives **60**, **61**, and **62**^{130,131}. In our case, however, the sugar analogues were the 2,3,4-triacetyl derivatives **63**, **64**, and **65** with CO₂Me in place of the CH₂OBn group. The reported methods are shown below:



Our precursors **63**, **64**, and **65** had to be synthesised from methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** using similar methods to those reported in the literature^{130,131}. We were disappointed when these attempted syntheses all failed, since the impression we gained from reading the papers was that the methodology is generally applicable and should have worked well for our targets.

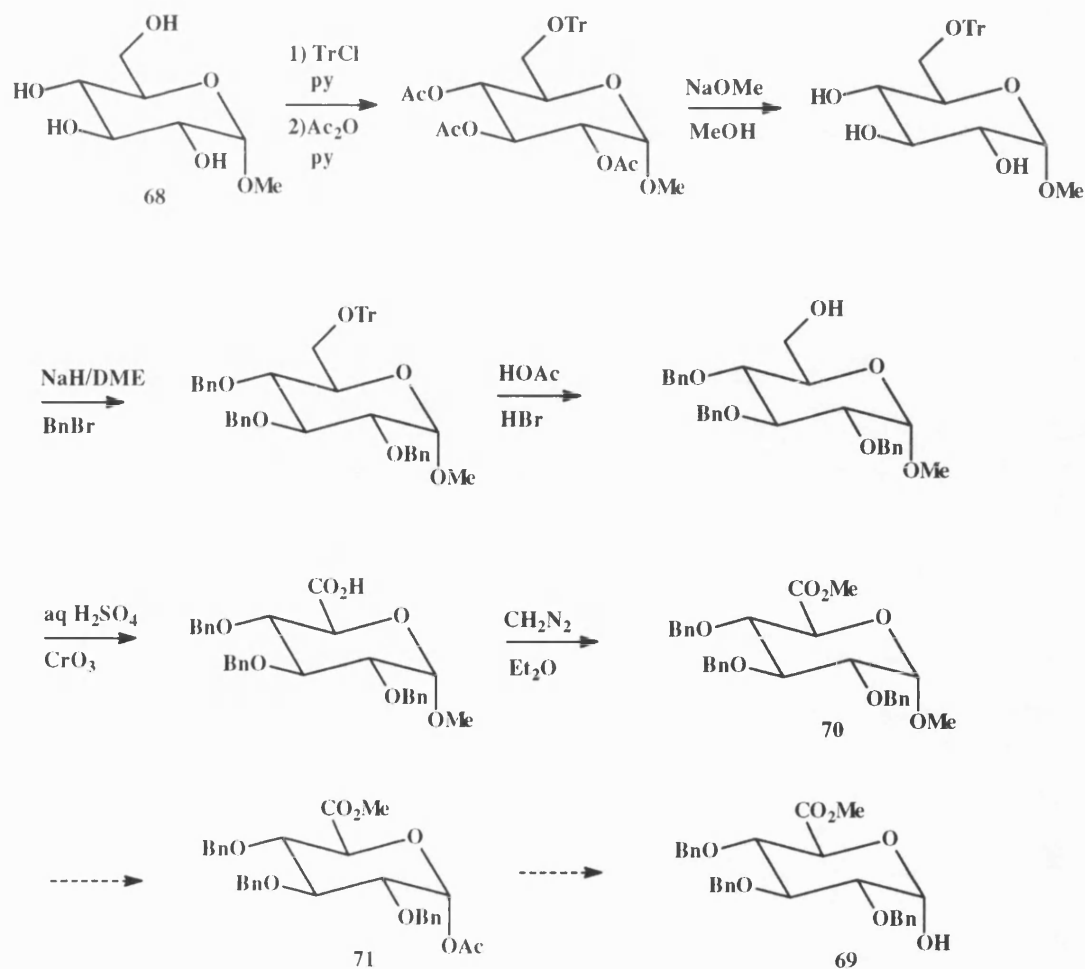
1.5 Coupling Attempts With Benzylated Sugars

The lack of reactivity we had experienced this far was likely to have been due to the presence of a C-2 acetoxy group which 'disarms' the glycoside¹³² and this caused us to examine non-acylated analogues, even though we recognised that this would result in the loss of stereo-control. There are a few exceptions where this does not occur, however, and there is a claim that the glycon methyl(trichloroacetimidyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate **66** reacts with androsterone **67** to yield the β -glucuronide almost exclusively¹³³.



Scheme 7.

We therefore set about the synthesis of **66** from methyl glucose **68** via methyl-2,3,4-tri-*O*-benzylglucopyranosyl uronate **69**, following the literature methods^{134,135}.



Scheme 8.

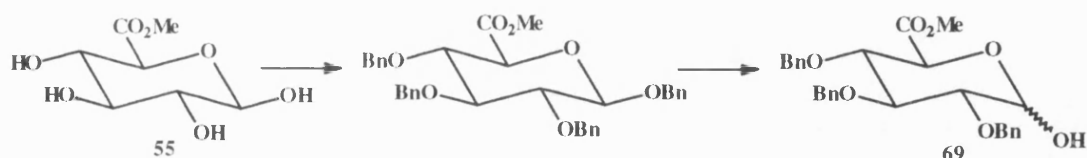
All the steps worked as planned up to the formation of methyl (methyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate **70**, however, the next reaction, namely *O*-demethylation/acetylation using glacial acetic acid and acetic anhydride to produce the 1-acetyl derivative **71**¹³⁵, failed. In our hands, the treatment returned only starting material. Even heating the reagents with 1.1 eq conc. sulfuric acid at 40°C for 24 hours was insufficient to effect the required reaction and after stirring overnight at 60°C the sugar was destroyed and subsequent treatment with sodium methoxide gave at least 6 compounds.

We also investigated other demethylation procedures. Trimethylsilyl iodide has been widely reported as a *O*-demethylating agent, but shows little selectivity between esters and ethers¹³⁶. This was indeed the case when we tried to use this reagent in either excess or a near stoichiometric amount. In both cases, t.l.c. showed the presence only of baseline material.

Boron tribromide has also been recommended for this type of demethylation¹³⁷ and we tried to use this in DCM as solvent. After one hour, t.l.c. analysis indicated complete conversion of the starting material to a compound with a higher R_F . However, when the reaction mixture was quenched with sodium hydrogen carbonate, t.l.c. analysis now showed that further conversion had occurred and only a baseline spot was visible. (N.B. our target runs with an $R_F \sim 0.3$ using the same mobile phase).

1.5.1 Alternative Syntheses of Methyl-2,3,4-tri-*O*-benzylglucopyranosyl uronate **69**

We decided that, since our attempts using this route were fruitless, another pathway was required. An alternative synthesis of the glucuronate **69** from glucose **72** is shown later in scheme 11. It utilises *O*-allyl protection, rather than *O*-methylation, in the key intermediate **73**¹³⁸. However, this is another tedious procedure involving 7 steps including a diazomethane methylation. In order to circumvent this we considered benzylating all four hydroxyl groups of methyl glucuronate **55**, followed by specific *O*-debenzylation at the anomeric position.



Scheme 9.

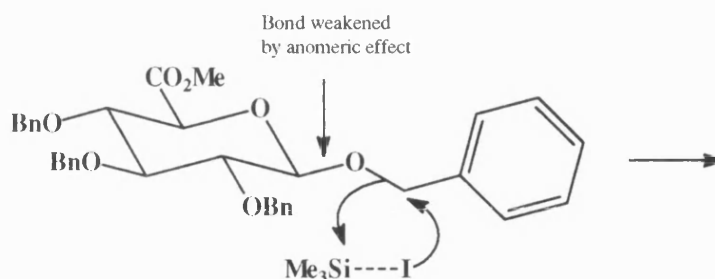
We attempted this first by reacting methyl glucopyranosyl uronate **55** with benzyl bromide and sodium hydride¹³⁹ in dimethoxyethane (DME) at reflux, but no reaction was observed after three days, possibly due to the lack of solubility of the carbohydrate tetra-sodium salt. The phase-transfer catalyst tetrabutylammonium iodide¹⁴⁰ was added and the reaction was continued for one day, however this did not cause any reaction to occur either.

The reaction was attempted in the more polar solvent DMF at 100°C and the sodium hydride and benzyl bromide were added in portions of 1.1 and 2.0 eq respectively to the solution of carbohydrate **55**. After 10 hours with only one of each portion added, no reaction was observed. Second portions were added and the reaction was continued, but again no new products were formed.

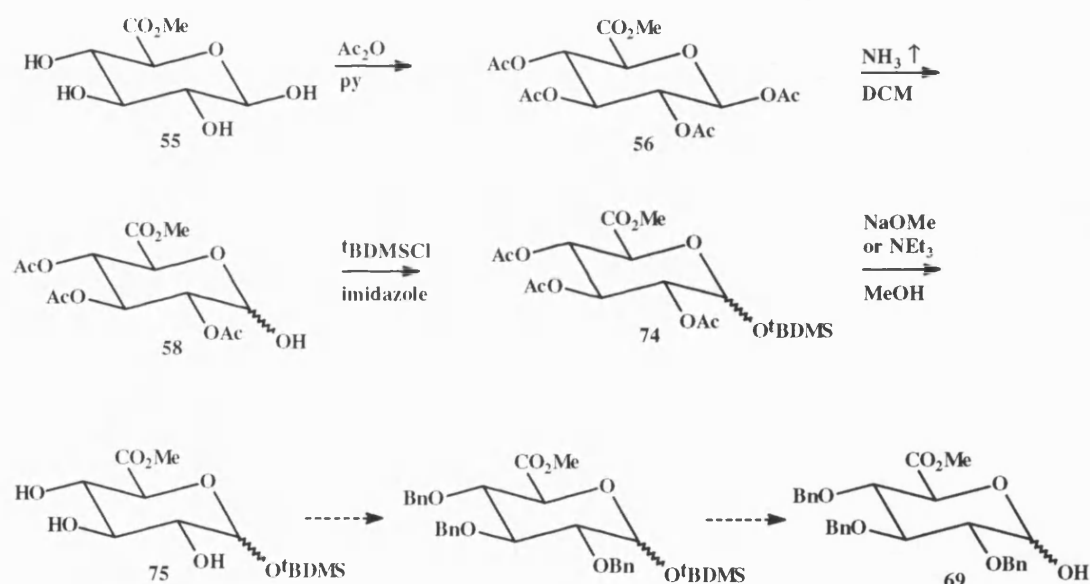
Also attempted was the tetra-*O*-benzylation of **55** using benzyl trichloroimidate and catalytic boron trifluoride etherate in DCM¹⁴¹. However, this was also unsuccessful with no conversion of the starting material.

Our concern over pursuing this work was tempered by the fact that *O*-debenzylation requires relatively harsh conditions and, after considering all the known techniques^{136,142}, it was obvious that the required specificity for the anomeric centre

could not be achieved. The anomeric effect only weakens the glycosyl bond and this is not broken during *O*-debenzylation, e.g.



Hence, our strategy was to use methyl-2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** and to protect the anomeric position with a 'butyldimethylsilyl group'¹⁴³.



Scheme 10.

Methyl tri-*O*-acetylglucopyranosyl uronate **58** was synthesised, as before, from glucurono-6,3-lactone **54**, but the previous two steps (bromination and hydrolysis) can be short-cut by a simple acyl hydrolysis step. This is performed by bubbling dry ammonia gas through a solution of methyl tetra-*O*-acetylglucopyranosyl uronate **56** in

cold DCM¹⁴⁴. *O*-Silylation of **58** was achieved using the reagents 'butyldimethylsilyl chloride (1.1 eq) and imidazole (3.0 eq) in THF¹⁴³ and purification was effected by extraction. This gave silyl glucuronate **74** in 92% yield.

Deacetylation of the product proved to be much more difficult than expected, but not because of silyl migration, as might have been suspected. Several techniques were tried and the yields are shown in the table.

Reagent	Solvent	Yield of 75 (%)
sodium methoxide	methanol dry	33
potassium carbonate	methanol/water 1:1	0
potassium carbonate	methanol/water 9:1	0
triethylamine	methanol dry	33
2M ammonia	methanol	25

The first choice of reagents for the reaction is catalytic sodium methoxide in dry methanol¹⁴⁵ since this should not affect the methyl ester functionality and product isolation is simple. However, in practice, treatment with 0.1 eq sodium methoxide gave only partial conversion (by t.l.c.) after one day and no further conversion with 0.2 eq present after a further two days. In both cases, we had evidence that at least two minor side products were forming but starting material was still present. Sonification

of the reaction mixture for a further two days caused no further conversion, but flash chromatography of the crude reaction product gave the *O*-deacetylated product **75** in 33% yield, while starting material **74** (only 2%) and by-products (10% of starting mass) were also recovered.

Consequently, other reagent systems were investigated. Aqueous potassium carbonate is known to be effective in deacetylation reactions, but it may also hydrolyse methyl ester functions¹⁴⁶. Since potassium carbonate is insoluble in methanol, some water is required, but when we used this base in a 1:1 mixture of methanol and water we found that the starting material was insoluble and was completely recovered. However, when a 9:1 mixture of methanol and water was used, the starting material was destroyed within 5 minutes.

Two other, lesser known techniques were also tried. Dry triethylamine (5 eq) in methanol¹⁴⁷ showed similar results to sodium methoxide, reaching a quick (< 1 day) but premature end-point, i.e. only partial conversion was achieved. Unfortunately, besides the assumed product spot, t.l.c. showed that four by-products were also present with similar R_F values to those obtained from the sodium methoxide reaction. Flash chromatography of the reaction mixture gave impure product **75** in 68% yield, starting material in 24% and the close running by-products as 18% of the starting mass. The R_F values of the by-products were too close to encourage us to make a determined effort to separate them. Eventually, compound **75** was crystallised from isopropyl ether affording the pure product in 33% yield as colourless prisms.

Another method using 2M ammonia (7 eq) in methanol (0.5M ammonia)¹⁴⁸ was examined. After four days reaction time this gave a greater conversion of the starting

material to the product than any of the other sets of reaction conditions, but also a greater level of decomposition products. When higher concentrations of ammonia were used, the decomposition processes were enhanced. Under the best conditions we only obtained a yield of 25% for product **75**.

After this we decided not to continue the investigation further. We accepted the low yield and next examined the *O*-benzylation of **75**. This also proved to be a very difficult process.

Originally, we reacted glucuronate **75** with benzyl trichloroacetimidate (4 eq)¹⁴¹ and boron trifluoride etherate (0.4 eq) in DCM at room temperature, but after 1 hour the reaction mixture contained at least 5 compounds. There was little change after 17 hours, even when more boron trifluoride etherate was added, and we were unable to isolate any tangible products from the reaction mixture. It is reported that boron trifluoride etherate does not always effect clean benzylation and the reaction products are frequently complex mixtures. Better results are claimed for the use of trifluoromethane sulfonic acid (triflic acid)¹⁴¹ promoted reactions, but we were concerned that such a strong acid might desilylate our compound. Notwithstanding this concern we attempted the benzylation using 11 eq benzyl trichloroacetimidate and 0.2 eq triflic acid in DCM. In order to minimise the probability of desilylation, the triflic acid was first added to a solution of benzyl trichloroacetimidate in DCM and stirred for 10 minutes before a solution of glucuronate **75** in DCM was added dropwise over half an hour. It was our premise that this slow addition would minimise the concentration of **75** present in the reaction mixture since *O*-benzylation should be almost instantaneous. In the event, however, a mixture of products was formed.

Other, more traditional methods for benzylation were also tried. The first of these employed benzyl bromide (3.5 eq) and sodium hydride (3.5 eq)¹³⁹ in dimethoxyethane (DME). After boiling the solution for 24 hours, t.l.c. indicated no conversion so further portions of benzyl bromide and sodium hydride were added and the reaction continued overnight. After this time, t.l.c. showed two, u.v. active spots with high R_F values. Flash chromatography of the reaction products gave both compounds as oils, but their n.m.r. spectra were incompatible with benzylated carbohydrates. The yields obtained were very low, so further work on these products was not continued.

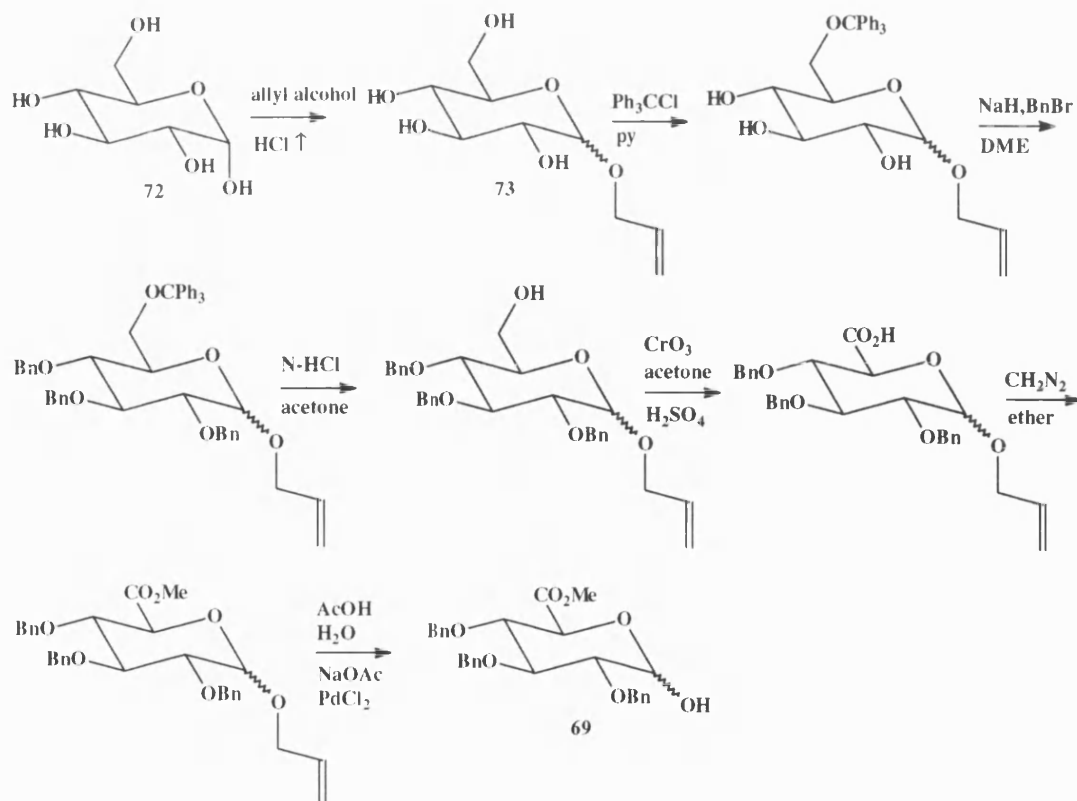
A similar reaction was attempted using DMF instead of DME as solvent, a choice forced upon us since we observed that glucuronate **75** was incompletely soluble in the latter solvent even at reflux. This, we thought, might have been partly responsible for the poor reactivity, in the event, however, this change was ineffectual and again no benzylation of **75** was observed.

At this point we felt that a change of tactic was necessary and we sought to increase the reactivity of the benzyl bromide by adding silver oxide to the reaction mixture¹⁴⁹. Thus, a solution of glucuronate **75**, silver oxide (4.5 eq) and benzyl bromide (4.5 eq) in DMF were reacted together at room temperature during 4 days. After this time, t.l.c. analysis showed 3 u.v. active spots and a large amount of starting material. The solution was stirred at 100°C overnight, but no further change was observed. After this time, more benzyl bromide (2 eq) was introduced and the reaction was continued but again to no avail. More additions of 10 eq of both silver oxide and benzyl bromide were made and the solution was stirred at 130°C for a further 24 hours. Again u.v. active spots were in evidence from t.l.c. but now these seemed much more prominent

than before. Flash chromatography enabled us to obtain trace amounts of crude samples of these materials, but there was no evidence that they contained carbohydrate units. It is known that benzyl bromide in the presence of Lewis acids can couple to form arylalkanes and arylalkenes and we assume that this is what these compounds are.

Yet another attempt at *O*-benzylation was made using benzyl chloride (9 eq) and sodium hydride (4.5 eq) in dimethylsulfoxide (DMSO)¹⁵⁰. This combination has been reported to promote the rate of this type of substitution reaction. To the mixture was added **75** in the same solvent, but once more no benzylation occurred, even though aromatic side products did form. In desperation we raised the temperature to 120°C for 8 hours at which point a strong smell of dimethyl sulfide was noted. An examination of the t.l.c. of the products showed that the desired alkylation had not occurred and only a baseline of fluorescent spots was observed.

Since the deacetylation and benzylation steps had been so disappointing, the alternative synthesis of the glucuronate **69** via allyl-glucose **73** was undertaken despite the number of steps required.

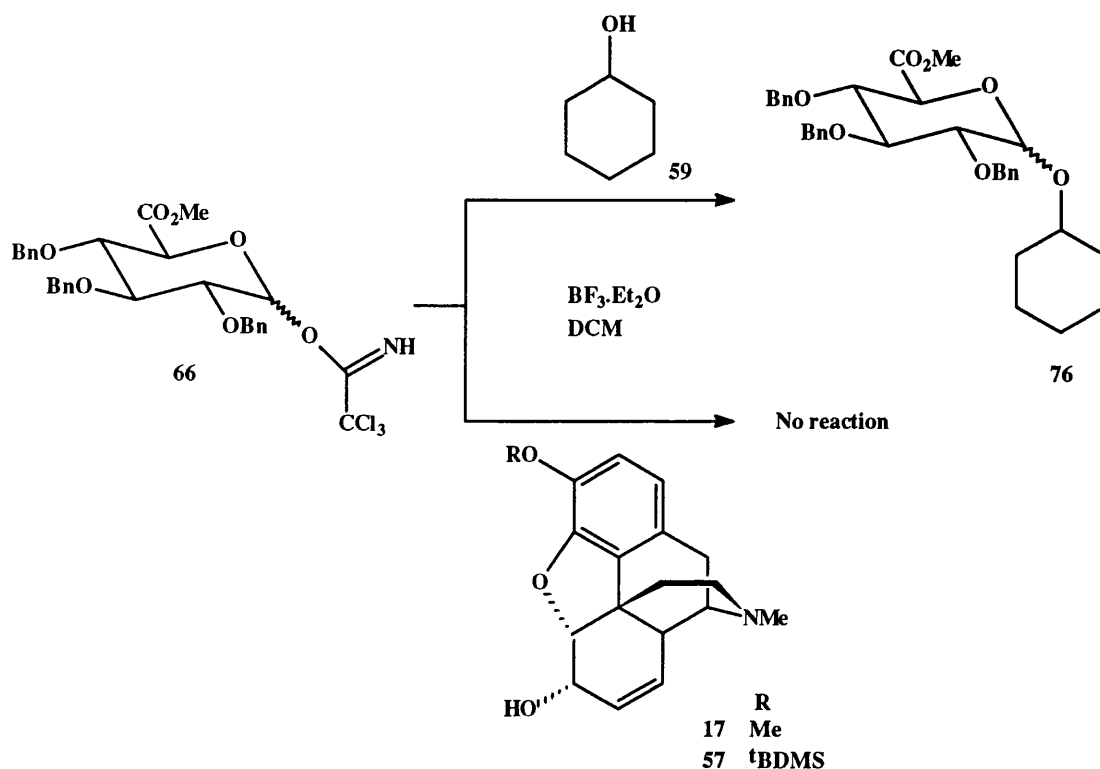


Scheme 11.

Allyl-glucose was prepared from glucose **72**¹⁵¹ on a large scale (100g) in 25% yield. The 6 remaining steps from allyl-glucose leading to **69** were all successfully followed in an overall yield of 20%. Finally, the trichloroacetimidate **66** was formed from **69** in 73% yield¹³³.

1.5.2 Attempted Couplings

Separate coupling reactions were attempted between the acetimidate **66** and the aglycons codeine **17**, silylmorphine **57**, and cyclohexanol **59**, using boron trifluoride etherate as a Lewis acid (scheme 12).

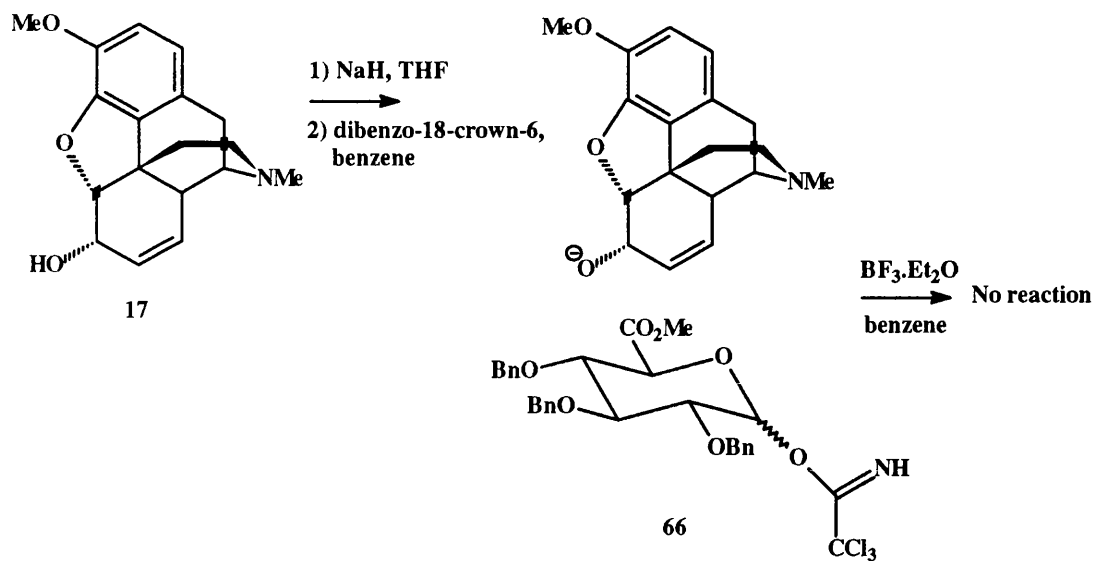


Scheme 12.

Of these reactions only cyclohexanol gave a positive result and a 12% yield of the coupled product methyl (cyclohexyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate **76**. Unfortunately, this product proved to be an anomeric mixture of 31:69 β : α . The analysis of the mixture is expedited since in the ^1H n.m.r. spectrum, the signal of the anomeric β -proton is exhibited as a distinctive doublet at around 5 p.p.m with 11.5 Hz

coupling constant, hence the β -1H integration was calculated and compared with the methyl ester peaks, which give a 3H integration total for both anomers. It should be noted that to achieve even this modest level of coupling it was necessary to allow the reaction mixture to rise from -23°C (the recommended temperature) to room temperature. It is possible that this extra warming may have adversely affected the stereoselectivity, since Schmidt claims that β selectivity is optimised at low temperature¹³³. We spent some time investigating this problem, but our results serve only to confirm that our reaction does not occur even at 0°C . The only conclusion to be gained from these experiments is that codeine **17**, and silylmorphine **57** are less nucleophilic than cyclohexanol, but even so cyclohexanol is still very unreactive under the conditions selected.

As a means of increasing the nucleophilicity, codeine **17** was treated with sodium hydride in THF to give the sodium salt, and to this reaction mixture was added dibenzo-18-crown-6 in benzene¹⁵² (scheme 13). It was hoped that this would solubilise the salt in the benzene phase. The reaction mixture was cooled to -15°C and the imidate **66**, also dissolved in benzene, was added, followed by boron trifluoride etherate (2.2 eq).

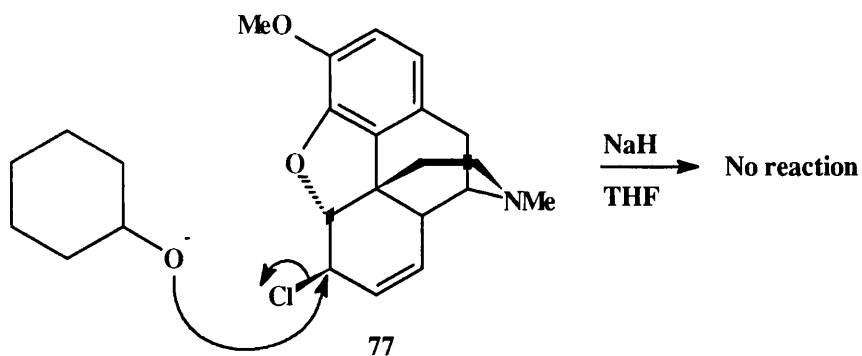


Scheme 13.

Unfortunately, the desired reaction was not observed, although this could be due to a variety of factors not least of all the incompatibility of the boron trifluoride etherate and the crown ether.

1.6 Nucleophilic Displacement of Chloride From α -Chlorocodide.

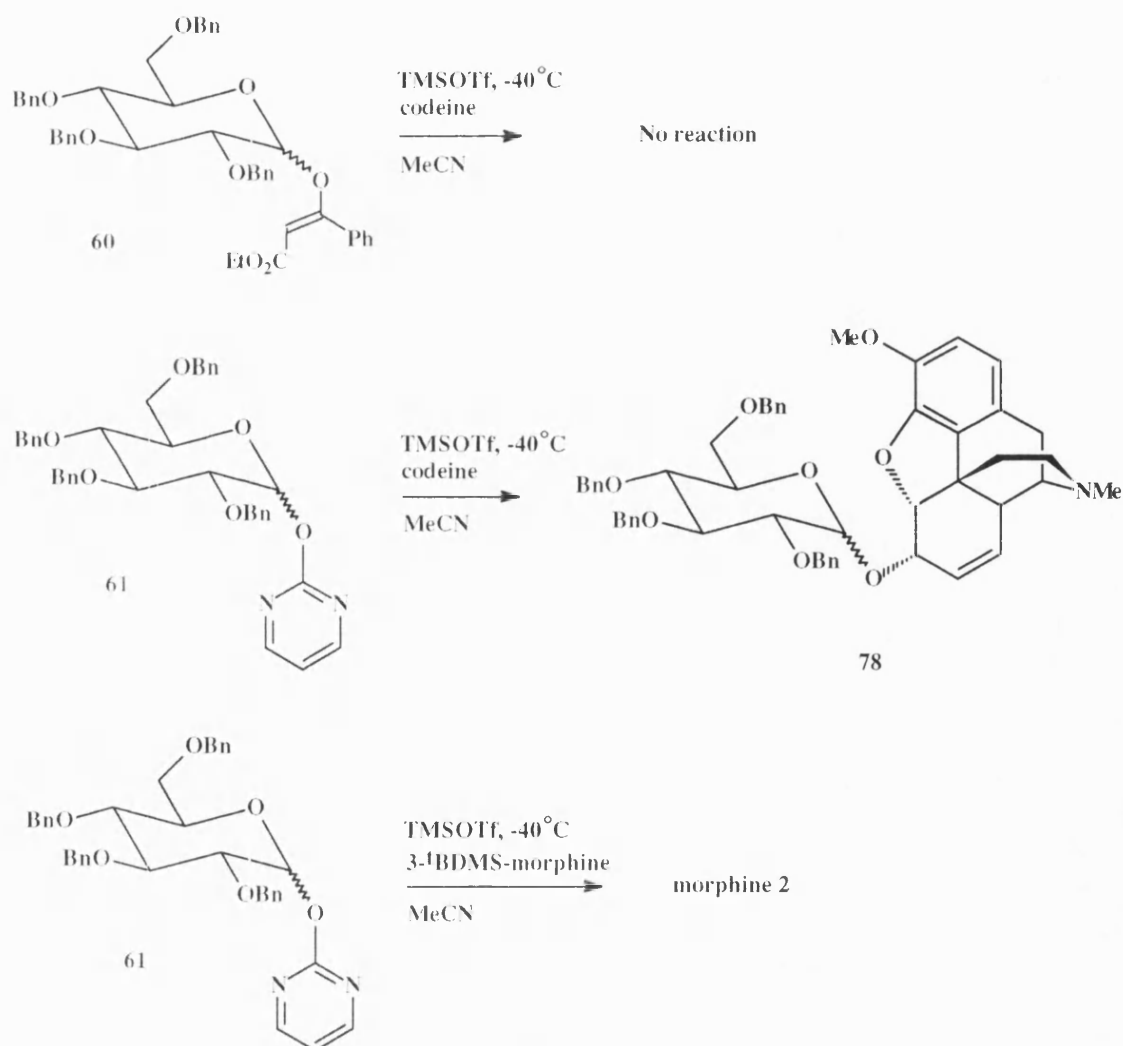
At this point, we investigated the possibility of using an electrophilic opioid which could be attacked by a nucleophilic carbohydrate hydroxyl group as shown:



α -Chlorocodide (6 β -chlorocodide) **77** was formed from the reaction of codeine and phosphorus pentachloride in 75%¹⁵³. As a model reaction we attempted to couple this mixture with cyclohexanol (sodium salt). A solution of **77** in THF was added dropwise to a solution of cyclohexanol and sodium hydride in THF at 0°C. We anticipated either direct S_N2 displacement of the halide ion giving a 6-ether linkage or a S_N2' reaction giving an ether coupling at C-8. Unfortunately, after stirring the reactants for 8 hours at 20°C no reaction occurred.

1.7 Attempted Glucoside Couplings.

The only possible way forward was to synthesise a suitably protected morphine-6-glucoside using a tetra-*O*-benzylglucose derivative such as 1-*O*-(2-ethylcarboxylate-1-phenylethenyl)-2,3,4,6-tetra-*O*-benzylglucose **60** and 1-*O*-(2-pyrimidyl)-2,3,4,6-tetra-*O*-benzylglucose **61**, both formed from methyl glucose **68**¹⁵⁴, activated with trimethylsilyl triflate as shown earlier in scheme 6^{130,131}.

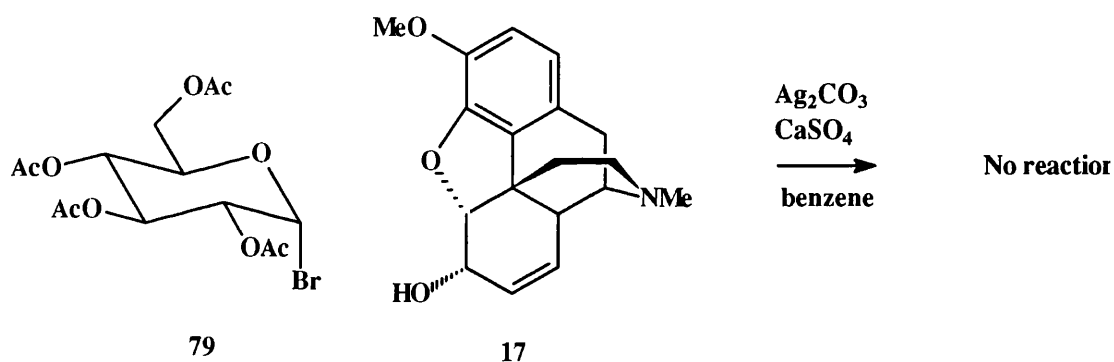


Scheme 14.

The attempted coupling between codeine **17** and the carbohydrate **60** resulted in the decomposition of codeine, while the carbohydrate was unaffected. However, coupling was achieved between codeine and carbohydrate **61** to produce the benzylated codeine glucoside **78** in 35% yield, but as a 1:1 anomeric mixture. Success at last, but the formation of this anomeric mixture posed a major problem to us since the anomers were extremely close running, ruling out chromatographic separation (bearing in mind the highly polar mobile phase which would be required). In addition, the low overall yield was disappointing. The same method was applied in an attempt to couple silylmorphine **57** and carbohydrate **61**, but this was totally unsuccessful and deprotection of **57** to morphine occurred. This, of course, is not unexpected in the presence of trimethylsilyl triflate.

1.8 Attempted Koenigs-Knorr Glucosidation

As with the glucuronidation, a stereoselective glucosidation using the Koenigs-Knorr reaction has been reported to occur between bromo tetra-*O*-acetylglucopyranoside **79** and codeine **17** in the presence of silver carbonate and anhydrous calcium sulfate in benzene¹⁵⁵. We attempted this reaction with our compounds, but failed and both starting materials were recovered.



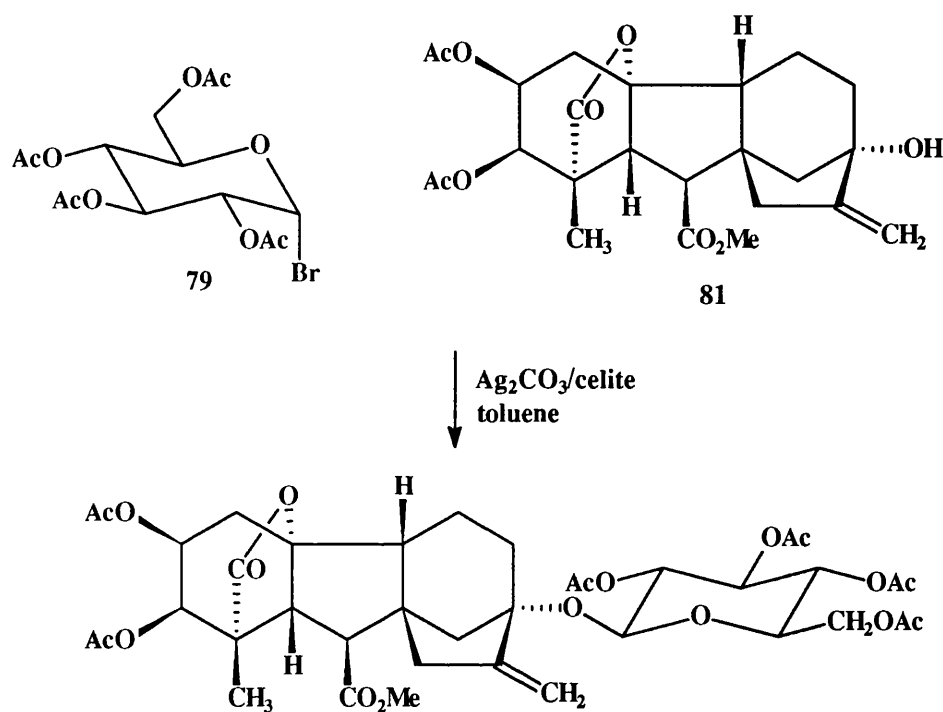
Scheme 15.

1.9 Attempted Enzymic Coupling

β -Glucosidation has been reported to occur in the coupling reaction of *o*-nitrophenylglucopyranoside **80** and an excess of a suitable alcohol in the presence of β -glucosidase at pH 5.0¹⁵⁶. We attempted to couple **80** and 8 eq codeine **17** under these conditions over 24 hours. Although t.l.c. indicated starting materials remaining, the existence of a new compound was also revealed. Work up and chromatographic purification of this compound gave a colourless crystalline solid, but a ¹H n.m.r. spectrum indicated that the product was simply a salt of codeine. This was confirmed by basifying a sample of the product and comparing it directly with codeine.

1.10 Couplings Using Silver Carbonate On Celite

Following an extensive literature search for acetyl-protected glycosyl coupling reactions, we found that the gibberellin **81** and bromo tetra-*O*-acetylglucopyranoside **79** could be linked by boiling them together in toluene in the presence of silver carbonate on celite¹⁵⁷ (scheme 16).

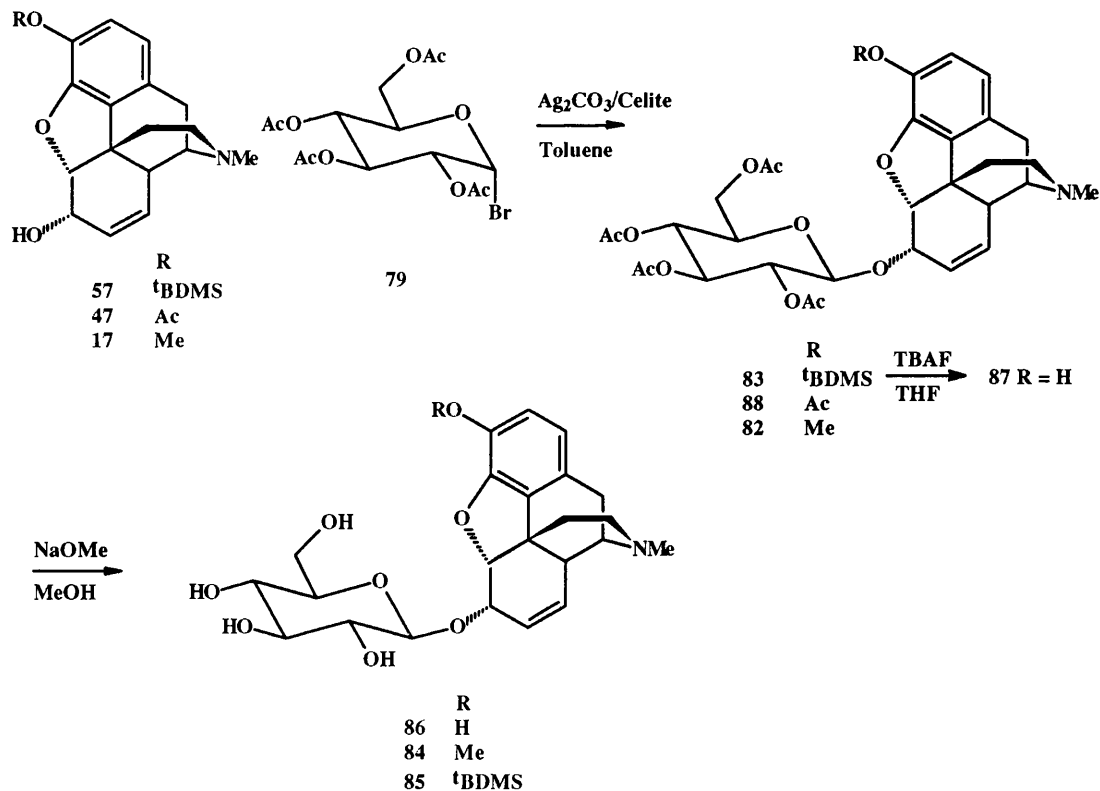


Scheme 16.

We were aware that the bromoglucoside **79** might be unstable, so in our first attempt at coupling this with codeine **17** in the presence of silver carbonate on celite, we restricted the temperature to 40°C (in boiling DCM). At this temperature no reaction took place, but at 112°C (toluene at reflux), we were pleased to note that two new compounds were formed. T.l.c. analysis showed these products to possess close R_F

values although higher than that of codeine. Clean-up of the reaction mixture, however, proved to be more difficult than we had hoped. Flash chromatography gave poor separation of the two new compounds and hence a yield of 30% was obtained for the major product. However, a dark trail which had also run up the entire length of the t.l.c. plate whilst monitoring the reaction, was still present; this despite filtering the solution prior to flash chromatography. As a result, codeine-2,3,4,6-tetra-*O*-acetylglucopyranoside **82** could only be deduced as a product by ^1H n.m.r. spectroscopy with contamination by other unidentified compounds.

We used the same procedure to couple silylmorphine **57** to bromoglucoside **79** and this gave (3-silylmorphine)-2,3,4,6-tetra-*O*-acetylglucopyranoside **83**, but in less than 13% yield after flash chromatography. It was still impure and was obtained as a brown oil.



Scheme 17.

1.10.1 Deprotection of Glucopyranoside Products (Scheme 17)

Subsequent deprotection with sodium methoxide did not proceed to completion and we were unable to obtain a single product in either case since chromatographic purification is not possible. Even on reversed-phase silica t.l.c., the products are eluted at the solvent front when 5% acetonitrile/water is used as the mobile phase. Despite our efforts to purify these deprotected products by extracting the impurities into ether, we still only obtained brown oils for codeine-6-glucoside **84**, and 3-'BDMS-morphine-6-glucoside **85** and both in less than 40% yields. Following desilylation of glucoside **85** using tetrabutylammonium fluoride (TBAF)¹⁴³, we were faced with a major problem since morphine-6-glucoside **86** was highly water soluble and could not be separated from the water soluble salts. Attempts were made to extract **86** from water into the polar organic solvents, chloroform or nitrobenzene, but these efforts were unsuccessful. We were, therefore, required to alter our strategy by performing the desilylation step prior to deacetylation.

The crude reaction mixtures containing glucosides **82** and **83** were extracted from ether into 1% aqueous acetic acid, before basifying and back-extracting into chloroform. T.l.c. analysis then confirmed the presence of opioids in the chloroform phase with the absence of carbohydrate by-products. The dark trail on the plates which characterised our earlier analyses was also missing. However, flash chromatography still gave poor separation of these opioids, but eventually we managed to obtain pure codeine tetra-*O*-acetylglucopyranoside **82** in 28% yield. Similarly, 3-silylmorphine tetra-*O*-acetylglucopyranoside **83** was obtained in 14% yield, and

subsequent desilylation of **83** with TBAF gave morphine-6-tetra-*O*-acetylglucopyranoside **87** in 20% yield. Since the overall yield of **87** was so low, the coupling was attempted between bromo tetra-*O*-acetylglucopyranoside **79** and 3-acetylmorphine **47** giving 3-acetylmorphine-6-tetra-*O*-acetylglucopyranoside **88** in 27%, thus allowing deprotection in one step.

Deacetylation of codeine glucoside **82** was achieved with sodium methoxide in methanol and the product was extracted from chloroform into water giving pure codeine-6-glucoside **84** with 75% yield. Similarly, deacetylation of morphine tetra-*O*-acetylglucopyranoside **87** to morphine-6-glucoside **86** was achieved with 95% yield.

1.10.2 Glucuronidation Using Silver Carbonate On Celite (Scheme 18)

With these successes in hand, this methodology was implemented in the coupling reactions of methyl (bromo-2,3,4-tri-*O*-acetylglucopyranosyl) uronate **48** with codeine **17** and 3-*t*-butyldimethylsilylmorphine **57**. At the end of the reactions we found that the acetic acid extractions were much less effective than they had been in the analogous glucoside reactions. This resulted in a yield of only 6% for codeine-6-methyl(tri-*O*-acetylglucopyranosyl) uronate **50**. Better results were obtained for 3-silylmorphine-6-methyl(tri-*O*-acetylglucopyranosyl) uronate **89** which was isolated in 36% yield after several acetic acid extractions. However, desilylation with TBAF only gave us an impure oil in 14%, even after flash chromatography. Fortunately, 3-acetylmorphine-6-methyl(tri-*O*-acetylglucopyranosyl) uronate **49** was synthesised from 3-acetylmorphine

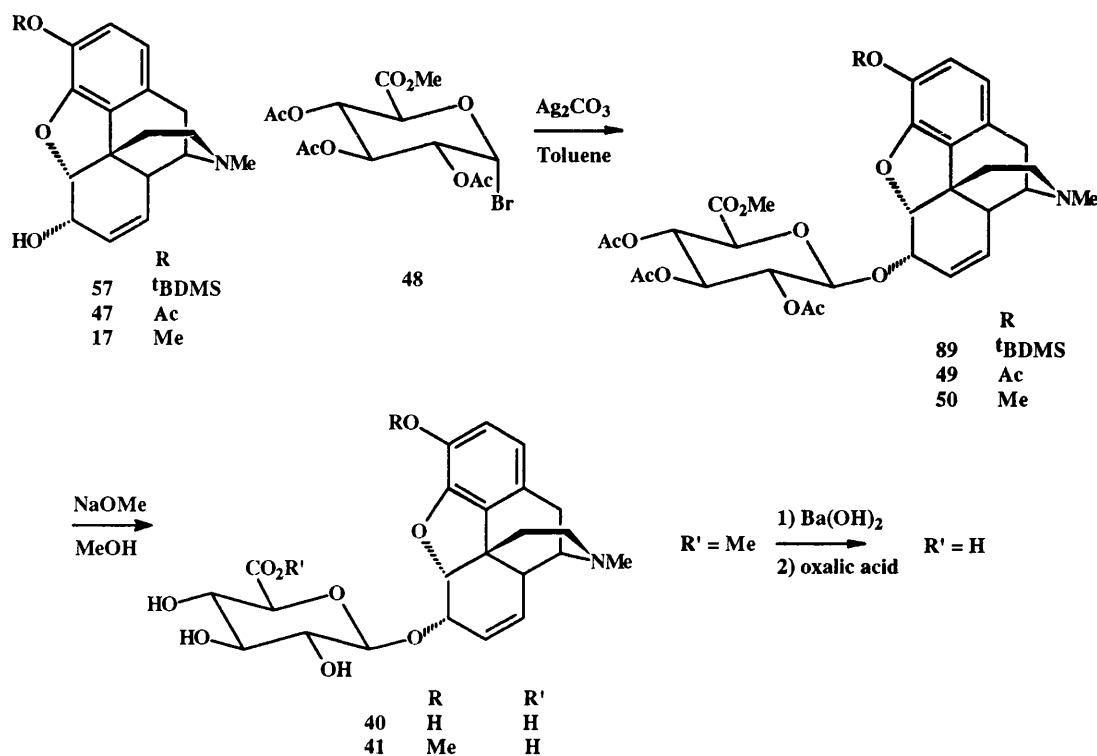
47 in 45% yield via ice-cold 0.5N HCl extractions. This method of isolation was also tried with codeine-6-methyl(tri-*O*-acetylglucopyranosyl) uronate **50**, but only a slight improvement in isolated yield (10%) was achieved.

% YIELDS	tetra- <i>O</i> - acetylglucopyranoside	methyl tri- <i>O</i> -acetylglucuronate
3- ^t BDMS-morphine	13	36
codeine	28	10
3-acetylmorphine	27	45

Further investigations on the coupling reaction have been carried out. Freshly prepared silver carbonate was mixed with celite (50:50 mixture) and used in place of the commercially available 'silver carbonate on celite' in the coupling of codeine **17** and methyl (bromo-2,3,4-tri-*O*-acetylglucopyranosyl) uronate **48**. Astonishingly, the t.l.c. analysis indicated a successful conversion, along with a side-product. Unfortunately, the work-up only gave a 7% yield of codeine-6-methyl(tri-*O*-acetylglucopyranosyl) uronate **50**, but this result compares reasonably with the 10% yield for the coupling using the commercial reagent.

Interestingly, when celite alone was substituted for silver carbonate on celite, t.l.c. analysis indicated that the side-product was formed in very small amounts but most of the starting material was still present. This side-product was recovered by

chromatography, although in only 3mg. ^1H n.m.r. and m.s. indicated the formation of codeine-6-acetate, presumably through displacement at a carbohydrate acetate centre, although this cannot be confirmed due to insufficient data.



Scheme 18.

Subsequent hydrolyses with sodium methoxide in methanol and barium hydroxide were carried out as detailed in the Yoshimura paper¹¹⁸. The intermediate morphine-6-methylglucopyranosyl uronate **90** was synthesised but only after using boiling sodium methoxide in methanol, in 68% yield but n.m.r. spectroscopy indicated a significant amount of morphine-6-glucuronide **40**, perhaps due to slight moisture presence allowing formation of sodium hydroxide which effects hydrolysis. Complete conversion of the ester **90** to morphine-6-glucuronide **40** was accomplished as described with aqueous barium hydroxide, which was removed by adding

stoichiometric oxalic acid, forming the insoluble barium oxalate which was filtered off. Evaporation gave a colourless crystalline solid in 90% yield. Although spectroscopic methods indicated that we had prepared pure morphine-6-glucuronide, the elemental analysis showed C, H, and N percentages only about half the expected values. This could only be due to the presence of barium salts since the elemental analysis of the coupled glucuronate **49** was correct.

As a result of these problems, alternative deprotection methods were sought. One such reported ester hydrolysis method uses a boiling aqueous suspension of Dowex acidic ion-exchange resin¹⁵⁸. In our case this would be attractive since there should be no inorganic salts remaining at the end of the hydrolysis.

The morphine glucuronate ester **90** was indeed converted to morphine-6-glucuronide **40** by boiling in water containing Dowex 50 (H). Conversion was confirmed by n.m.r. spectroscopy but, as before, the elemental analysis gave values much lower than expected.

Next, we attempted to hydrolyse all the acetyl and methyl ester protecting groups on our fully protected morphine glucuronate **49** using the above method with Dowex resin, thereby giving us deprotection in one step. This reaction proceeded much slower than the previous hydrolysis and t.l.c. analysis only indicated partial reaction. Even after 24 hours at reflux, it was still difficult to ascertain to what extent the deprotection had proceeded. The reaction products have similar retention indices on t.l.c. and are poorly resolved, however, ¹H n.m.r. (D₂O solvent) and m.s. spectra of the recovered material indicated that the hydrolysis of the methyl ester had occurred but the acetate groups had largely been unaffected.

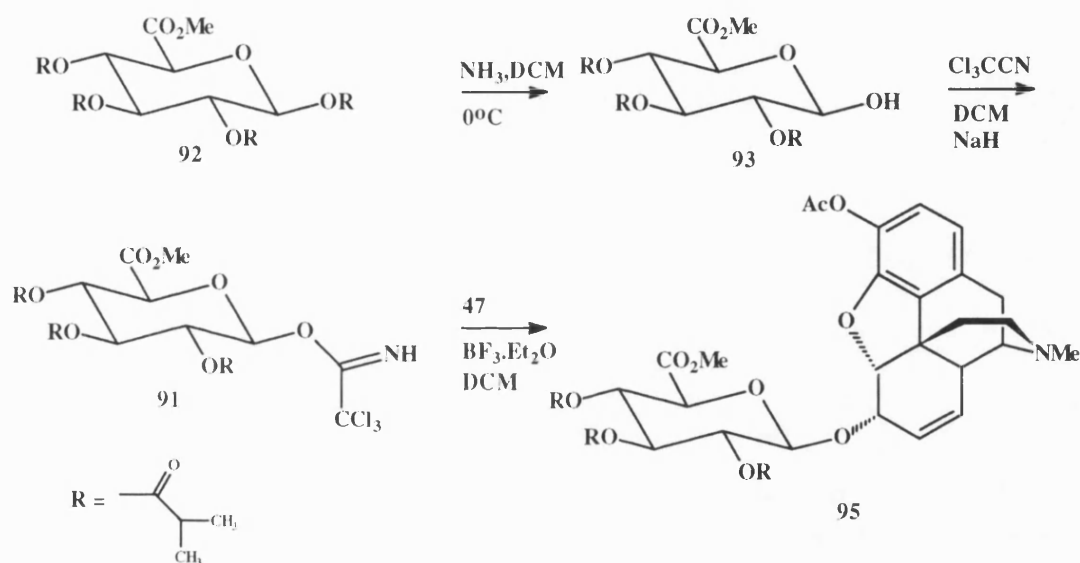
Since esters can be hydrolysed in acidic or basic conditions, we decided to try using a strongly basic ion-exchange resin instead, such as Amberlite IRA-410. After boiling the glucuronate **49** in an aqueous suspension of this resin for 3 days, the ^1H n.m.r. spectrum of the recovered material confirmed that hydrolyses of methyl ester had taken place as well as cleavage of all but one of the acetate groups. The product from this reaction was taken up in methanol and ammonia (2M) and left to stand for 2 days, but on work up a pure compound could not be isolated from the reaction mixture.

The procedure was repeated for the codeine glucuronate **50**. After boiling in water in the presence of Amberlite resin for 12 hours, t.l.c. showed conversion to a material with lower R_F value. To the reaction mixture was added concentrated ammonia¹⁴⁸ (giving a 2M solution) and methanol. After standing for 2 days, work-up of the reaction mixture gave a residue which was taken up in 1% acetonitrile/water and eluted through a Water Sep-pak C-18 cartridge with similar solvent mixture as the mobile phase. From the eluate the desired codeine-6-glucuronide **41** was recovered pure in 35%, after freeze-drying.

Sodium hydroxide should give faster hydrolysis of the protecting groups, whilst giving sodium acetate as the co-product. The latter should be less lipophilic than ammonium acetate, and therefore should be easier to separate on the C-18 cartridge. This was realised in practice and when codeine tetra-*O*-acetylglucopyranoside **82** was treated with sodium hydroxide (5 eq) in water for 10 minutes, quenching with acetic acid and purification using the C-18 cartridge gave pure codeine-6-glucoside **84** in 68%.

1.11 Alternative Claims

During our investigations, a patent application by Ultrafine was submitted in which an alternative synthesis for morphine-6-glucuronide was claimed. This utilises a coupling between methyl(trichloroacetimidyl-2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **91** and 3-acetylmorphine **47**¹⁴⁴ (scheme 19). Note, the protecting groups are isobutanoyl rather than acetyl in this case. The reported route is shown:



Scheme 19.

We investigated this route very carefully, achieving a synthesis of methyl (1,2,3,4-tetra-*O*-isobutanoylglucopyranosyl) uronate **92** in 43%, but failing to react this to yield **93** with a solution of ammonia in DCM at 0°C, as described. However, when we used a continuous flow of ammonia at 20°C we were able to recover methyl (2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **93** in 60%. A procedure for synthesising methyl(trichloroacetimidyl-2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **91** was also

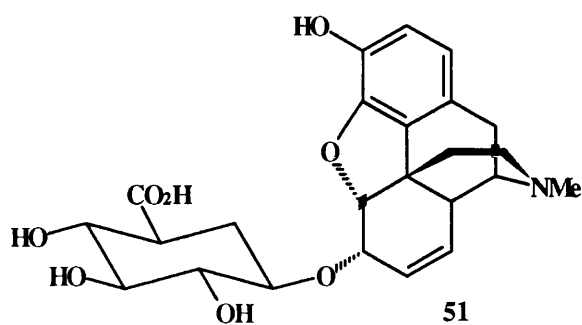
claimed, in which the product is obtained as colourless needles from isopropanol. However, when we attempted to reproduce this methodology we found that the expected product **91** had reacted with isopropanol to give methyl (isopropyl-2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate in 25% yield. The reaction was repeated without crystallising, but instead purification gave us the desired product **91** in 75% yield as a colourless oil, which crystallised on standing.

Reaction between 3-acetylmorphine **47** and 2 eq imidate **91** in DCM in the presence of 2 eq boron trifluoride etherate was achieved, although t.l.c. monitoring revealed the presence of at least two other compounds and unreacted 3-acetylmorphine. Work up, as described, and chromatographic purification gave 3-acetylmorphine-6-methyl-(2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **95** in 15% yield.

Deprotection was performed by treating **95** with 5% sodium hydroxide in methanol, neutralising with acetic acid to pH 5.5, as described. However, the product did not precipitate and we only obtained crystals of sodium salts leaving morphine-6-glucuronide **40** in solution with the remainder of the sodium salts.

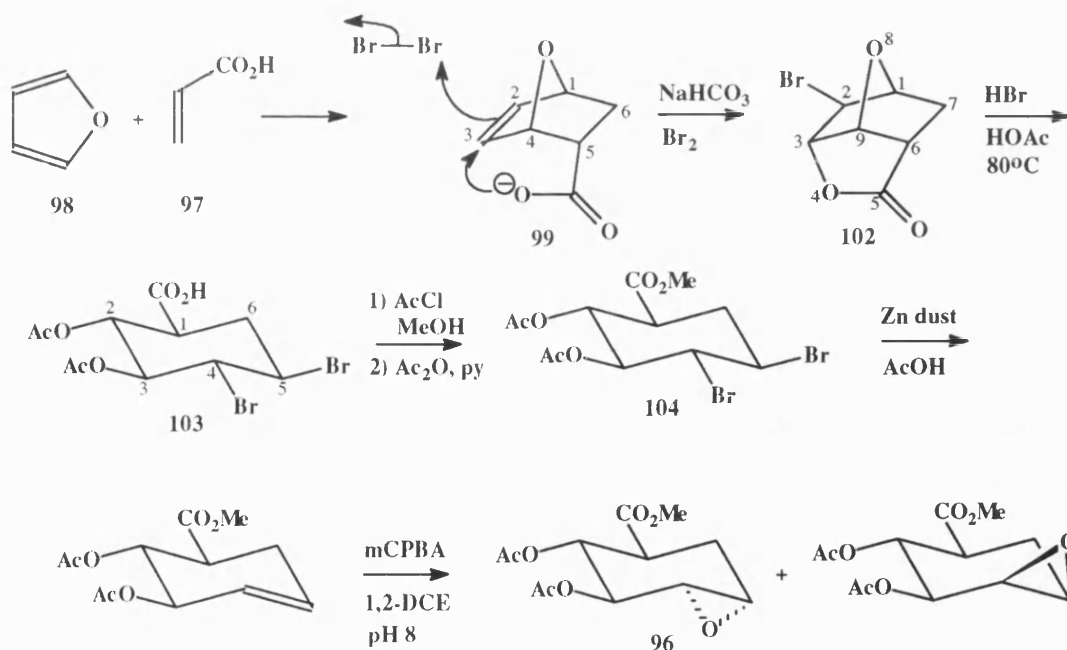
2 CH₂ ISOSTERE TARGETS

2.1 Attempted Synthesis of Morphine-6-pseudoglucuronide **51**



2.1.1 Pseudosugar Methodology

Following an extensive literature search we found several examples of carbohydrate CH₂ isosteres, referred to as 'pseudosugars'¹⁵⁹. One example gives the synthesis of a pseudosugar **96**, which simulates a protected glucuronate precursor¹⁵⁹. All compounds described are racemic:



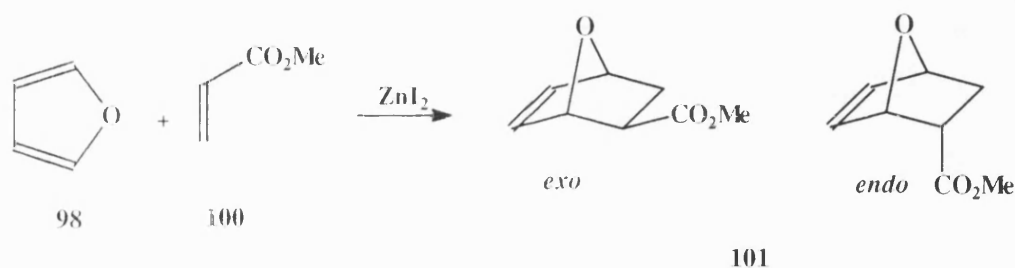
Scheme 20.

The pseudosugar **96** is an epoxide which may possibly be ring opened with a suitable morphine derivative, but, in addition, opens the door to a range of other pseudoglucuronate precursors such as a substituted cyclohexanol or cyclohexyl bromide. The coupling to a morphine derivative might give separable diastereomers or alternatively a non-racemic route to pseudosugar **96** could be possible if the first step (Diels-Alder) is performed in an enantioselective fashion.

Since the route involves several steps (scheme 20), we attempted this work in parallel to our pursuit of an effective coupling technique for pseudoglucuronates and opioids.

2.1.2 Synthesis of Epoxide Precursor

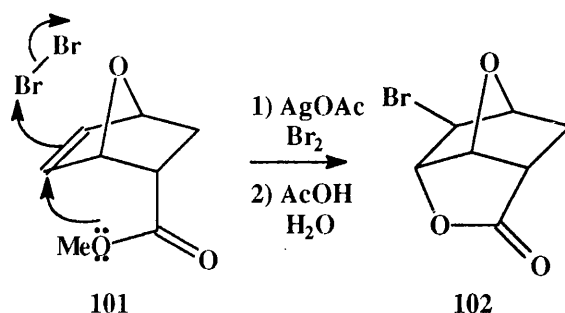
The first step in the reported procedure was the Diels-Alder reaction between acrylic acid **97** and furan **98** to produce 7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid **99**, mostly as the required *endo* product¹⁶⁰. However, this method has a reaction time of more than 2 months! We therefore searched for an alternative method, perhaps utilising a Lewis acid catalyst and discovered that the reaction of furan with methyl acrylate **100** can be performed in just 2 days in the presence of anhydrous zinc iodide at 40°C, but only gives a 1:2 *endo:exo* ratio for the product 7-oxabicyclo[2.2.1]hept-5-ene-2-methylcarboxylate **101**¹⁶¹.



Scheme 21.

Since the *exo* is the thermodynamic product, we attempted this reaction at the reduced temperature of 4°C and, after 2 days, t.l.c. analysis indicated partial conversion. The reaction was continued at 20°C for a further 2 days, after which time t.l.c. indicated virtually complete conversion. After work-up, analysis of the n.m.r. spectrum for the product mixture, recovered in 35% yield, indicated a 2:1 *endo:exo* ratio. No separation of these epimers was attempted at this stage since the saponification and lactonisation steps are performed in basic conditions in which further epimerization may occur.

Despite the expected ease with which the hydrolysis and lactonisation steps should be carried out, we first attempted to short-cut these steps by performing a wet Prévost reaction¹⁶².



However, none of the starting material was converted. The only change was that slow epimerisation of the starting ester **101** occurred giving a higher ratio of the *exo* compound.

Saponification of **101** has been reported to occur using aqueous sodium hydroxide in 50%. Also noted in this report was a lack of complete conversion and small recovery (<1%) of *endo* ester. Instead, we first tried lithium hydroxide in a mixture of methanol and water as reagent and achieved a 91% yield of the carboxylic acid **99**, but still as a mixture of epimers.

Bromolactonisation of **99** to the lactone **102** was achieved using bromine in aqueous sodium hydrogen carbonate, as reported, but in 55% compared with the literature yield of 91%. However, this result may be expected when considering the presence of 33% *exo* carboxylic acid in the starting material, since only the *endo* acid is lactonised. This was born out by analysis of the reaction mixture by t.l.c., which showed a high level of starting material remaining on the baseline. The reaction was repeated with sodium hydroxide in place of the sodium hydrogen carbonate in the hope that the proton

located α to the carboxyl group would be labile under these conditions and an equilibrium between the two epimers would be set up (figure 4).

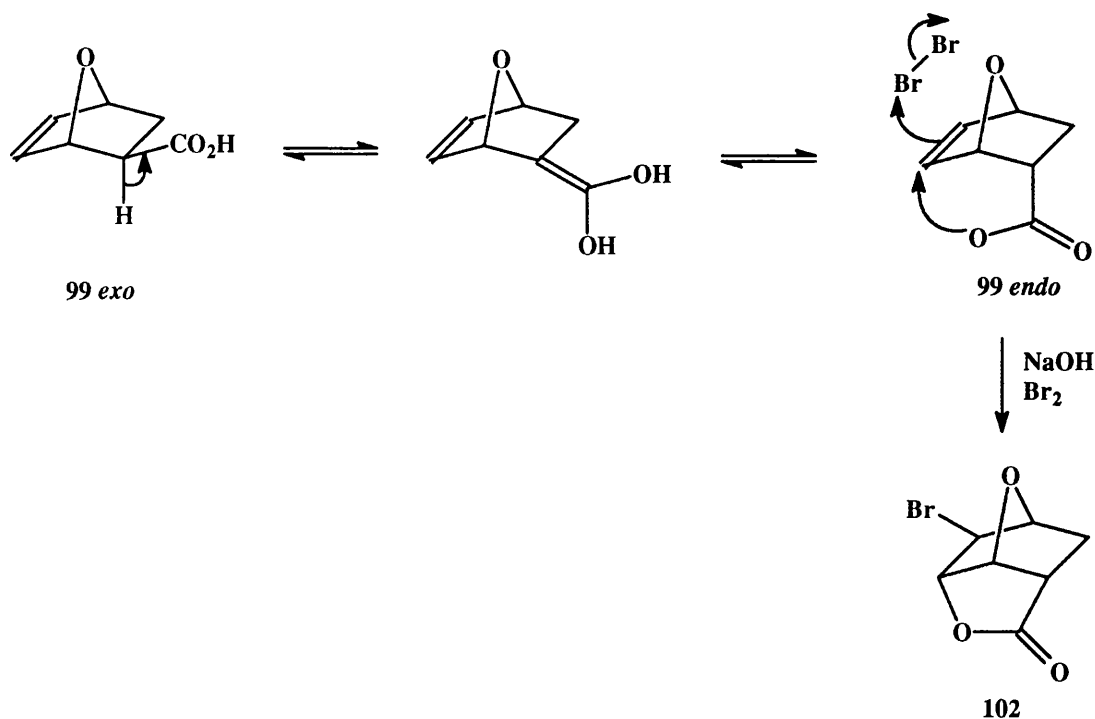


Figure 4.

However, no improvement was obtained with a recovery of 48%.

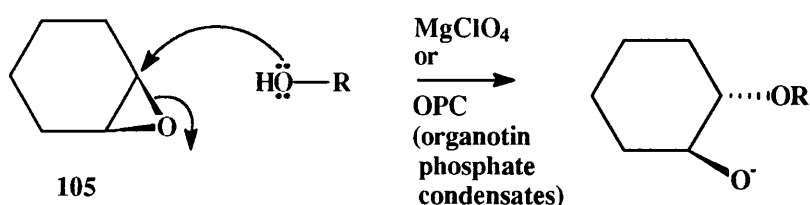
Worse still, our attempt to reproduce the reported conversion of the bromolactone **102** to the dibromocyclohexane **103** gave only an 8.4% yield against the literature claim of 64%.

Further problems beset us in the esterification of the acid **103** to the ester **104**. Our yield was 66% against the literature claim of 96%. As a result the synthesis was put on hold until we could establish if the nucleophilic ring opening of the epoxide would succeed.

2.1.3 Investigation of Coupling Methodology

i) Attempted Couplings From Epoxide Opening

We were required to find a model reaction to simulate this process and, considering our epoxide target above, our first attempts were made using cyclohexene oxide **105** since epoxides may show reactivity towards alcohols.



The reported procedures make use of the nucleophilic hydroxyl group to attack at one of the centres of the activated epoxide. Activation of the epoxide has been claimed with both magnesium perchlorate¹⁶³ and organotin phosphate condensates (OPC)¹⁶⁴⁻¹⁶⁶. Despite the reported high ratio (10:1) of alcohol to epoxide starting materials, it was important that we achieve a higher yield based on the morphine derivative, and therefore we only used a 1:1 ratio of the starting materials. Attempting to link 3-acetylmorphine **47** to the epoxide **105** in the presence of 1 eq magnesium perchlorate, however, only had the effect of deacetylating **47** to morphine.

Methodology using OPC has been heavily reported¹⁶⁴⁻¹⁶⁶. The catalyst was prepared as described from dibutyltin oxide and di-*n*-butylphosphate¹⁶⁷ and was subsequently used in an attempt to couple the silyl-morphine **57** and the epoxide **105** by boiling in petroleum

ether 60-80° for 4 days. T.l.c. analysis showed that no conversion had occurred, however, and the starting materials were still present. It is known, however, that epoxide openings of this type are often reversible with attack from the alkoxide to reform the epoxide, a step which is entropy favoured.

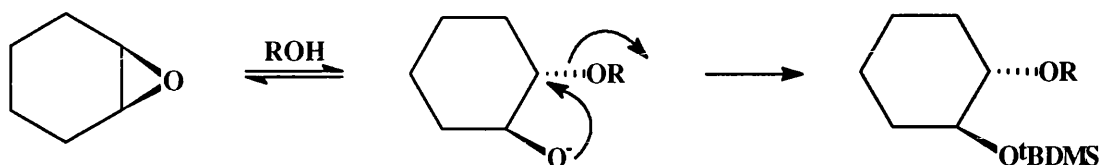


Figure 5.

The reaction was repeated until, after 4 days, 1 eq ^tBDMS chloride was added to trap any alkoxide which may be formed in an equilibrium process. After this the reaction was continued for a further 8 hours. However, this had no effect on the outcome and we observed no reaction.

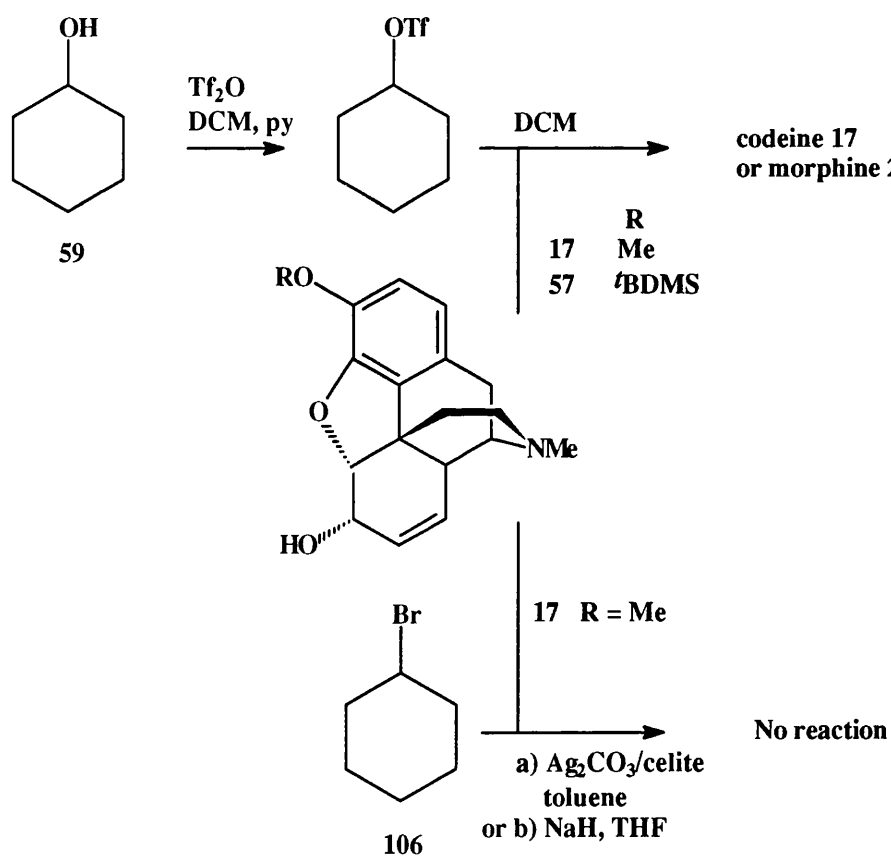
In case some process was occurring which prevented rejuvenation of the catalyst, the above attempt was repeated with 1.3 eq OPC present, but again this did not bring about a reaction.

Rather than activating the epoxide, we turned our strategy to activating the silyl morphine **57** by forming the sodium salt using sodium hydride in THF. The mixture was stirred for 2 hours but t.l.c. analysis showed no conversion, so the mixture was boiled for 6 hours. This time morphine was recovered in ~80% showing that *O*-desilylation is a dominant reaction.

ii) Attempted Ether Couplings of Opioids With Cyclohexanol and Cyclohexyl Bromide

Rather than pursuing other reported methods for opening epoxides with alcohols, we turned our efforts to other reactive electrophile possibilities (scheme 22).

The first of these was carried out using cyclohexanol **59**, converted *in situ* to the highly reactive triflate¹⁶⁸ which was reacted with silyl morphine **57**. T.l.c. analysis showed that a complicated mixture formed immediately but after 20 minutes, a single spot was present at lower R_F . This was later shown to be morphine, however.



Scheme 22.

The reaction was repeated for codeine **17** using 3 eq pyridine to remove unwanted triflic acid. However, t.l.c. analysis indicated no reaction and only codeine was recovered.

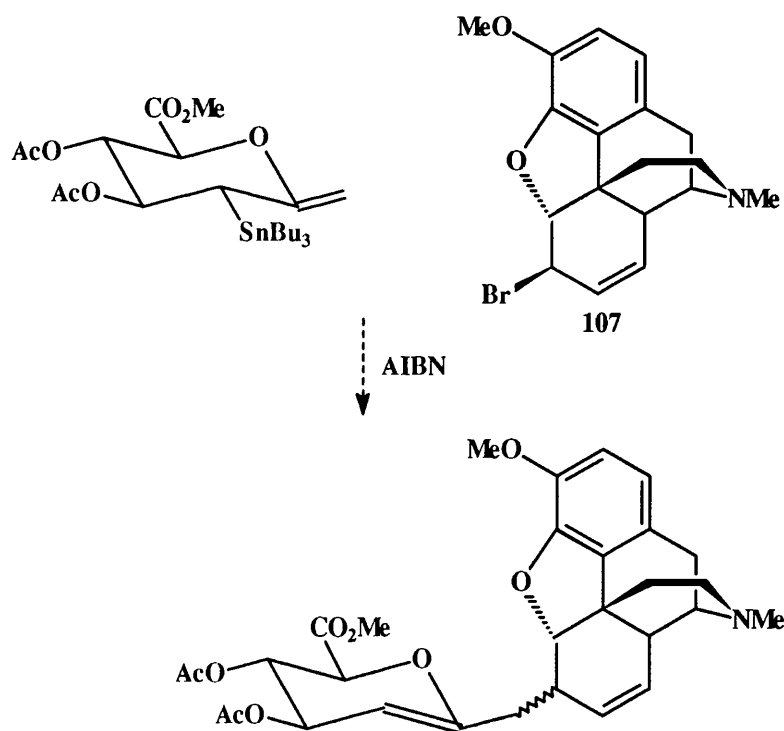
Also tried was the reaction between codeine and cyclohexyl bromide **106** in toluene in the presence of silver carbonate on celite which had given us previous success in bromide displacements. T.l.c. analysis indicated the presence of several compounds but also one main compound consistent with codeinone.

An attempt was also made to couple **106** and the sodium salt of codeine **17** formed by the action of sodium hydride in THF. However, no reaction could be seen by t.l.c. either after stirring at 20°C for 12 hours or by boiling for 5 hours.

As a consequence of these disappointing results, we abandoned this line of research to pursue another goal, as shown below.

3. C-Glucuronide Target 105

Our target here was to form a C-C link between morphine and glucuronic acid. Ideas for the coupling step were limited since relatively little work has been performed in the area of C-glycosides. Of great interest to us was tin radical chemistry¹⁶⁹, and in particular, a method which may give us such a linkage with a β orientation on the glucuronide unit and α orientation on the morphine unit. An example of the precursors we had in mind is shown below.

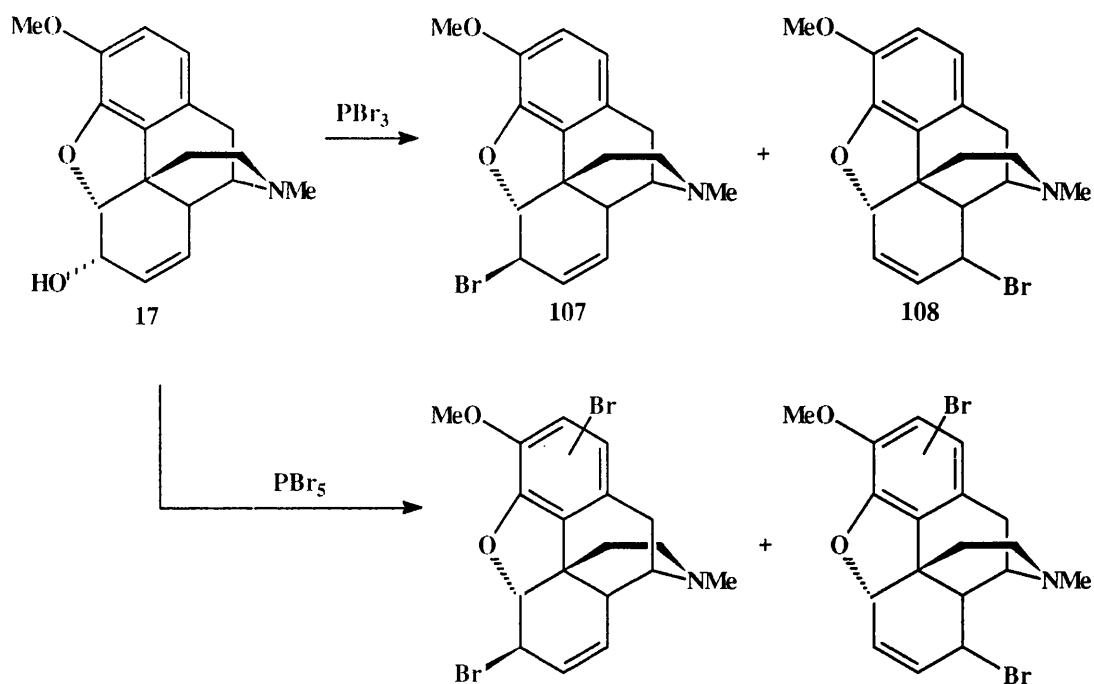


Our concern for this type of reaction is the specificity of radical coupling in the opioid moiety with respect to the allylic system, since rapid equilibrium following radical

generation is highly probable. Specificity for either the 6- or the 8- position is likely, however, with the steric bulk from the morphine structure. Prior to synthesis of a glucuronate precursor it was necessary to obtain an effective method and our initial precursor requirement was to obtain α -bromocodide (6 β -bromocodide) **107**.

Also of interest to us was a claim for codeine alkylations using an appropriate alkyl lithium cyanocuprate¹⁷⁰ and 6-mesyl-codeine or 6-mesyl-isocodeine.

Since time was against us, these ideas can only be described for future work and our only achievement was to confirm a useful procedure for the synthesis of α -bromocodide (6 β -bromocodide) **107**. The only cited literature method is that of Schryver and Lees in 1901 using phosphorus tribromide¹⁷¹, in which the correct structure could not be deduced due to the lack of available data at that time. Since we have already synthesised α -chlorocodide in high yield using phosphorus pentachloride, our first attempt was made using phosphorus pentabromide in a similar way. Unfortunately, however, we could only achieve the formation of a mixture of dibromides of the type shown, in 69%.



Scheme 23.

The orientation of the phenolic bromide could not be deduced although a 1-bromo compound has been produced previously by Gates and Shepard¹⁷⁰.

Instead, we followed the reported method using phosphorus tribromide to give α-bromocodide **107** and β-bromocodide (8β-bromocodide) **108** as a 1:1 mixture which is difficult to separate by chromatography. Partial separation was achieved giving α-bromocodide **107** in 11% yield and β-bromocodide **108** in 3% yield.

C. EXPERIMENTAL

All solvents were dry and distilled before use. 'Petroleum ether' refers to petroleum ether boiling in the range 60-80°C.

Flash chromatography was performed using Amicon Matrex 60Å silica gel under medium pressure using a small hand bellow.

Thin layer chromatography (t.l.c.) was performed using aluminium backed 250µm silica gel plates containing fluorescent indicator. Visualisation was achieved by illumination under short wavelength (254nm) u.v. light when possible. Plates were developed by treatment with a 0.5% (w/v) aqueous solution of potassium permanganate, followed by warming of the plate.

Melting points (m.p.) were determined on Electrothermal Mk III apparatus and are uncorrected.

Elemental micro-analyses were carried out using a Carlo-Erba 1106 Elemental Analyser.

Optical rotations were measured using a Perkin-Elmer 141 polarimeter with concentration (c) expressed in g/100 cm³.

Infrared spectra were recorded in the range 4000-600 cm⁻¹ using a Perkin-Elmer 1310 spectrophotometer and peaks are reported in wavenumbers (cm⁻¹). Samples were prepared as chloroform solutions unless otherwise stated.

¹H and ¹³C nuclear magnetic resonance (n.m.r.) spectra were recorded on a Jeol GX270 (270MHz) spectrometer. For ¹³C, operating frequency was 67.8 MHz, using

90 and 135 DEPT pulse sequences to aid multiplicity determinations. Samples were prepared in solutions of CDCl_3 unless otherwise stated.

δ values are expressed as parts per million (p.p.m.) downfield from tetramethylsilane internal standard.

Mass spectra were recorded on a VG 7070E mass spectrometer.

δ_{C} assignments for opioid carbons were based on other literature findings¹⁷³.

For opioid glycosides, assignments for carbohydrate nuclei are in **bold type**.

1. Synthesis of methyl glucopyranosyl uronate **55**

D-glucurono-6,3,lactone (8.0g, 44mmol) was added portionwise to a stirred solution of sodium hydroxide (40mg, 1.0 mmol) in methanol (80ml). On complete dissolution, the yellow solution was stirred for 12 hours. T.l.c. analysis indicated complete conversion and the solution was concentrated and dried *in vacuo* to an orange syrupy solid (9.05g, 96%).

R_F: 0.8 (mobile phase = 50% methanol/chloroform);

m/z (C.I.) 209 ($\text{M}^+\text{+H}$), 191 ($\text{M}^+\text{--OH}$).

2. Synthesis of methyl 1,2,3,4-tetra-*O*-acetylglucopyranosyl uronate **56**

A solution of methyl glucopyranosyl uronate **55** (9.0g, 43mmol) in pyridine (50ml) was stirred at -10°C and acetic anhydride (6.0ml, 64mmol) was carefully added. The solution was stirred at 20°C for 24 hours after which, t.l.c. analysis indicated complete conversion. The mixture was poured onto ice-water and extracted into chloroform (4x). The combined extracts were washed with 1M hydrochloric acid (100ml), dried over sodium sulfate, and concentrated *in vacuo* to a black oil which was crystallised from isopropanol at 4°C. This and two further crystallisations from the mother liquor afforded a colourless crystalline solid (12.5g, 77%).

R_F: 0.8 (mobile phase = 30% methanol/chloroform);

δ_H 5.77 (1 H, d, *J* 7.7, C¹-H), 5.33 (1 H, t, *J* 9.0, C³-H), 5.24 (1 H, t, *J* 9.0, C⁴-H), 5.15 (1 H, t, *J* 7.9, C²-H), 4.20 (1 H, d, *J* 9.3, C⁵-H), 3.75 (3 H, s, ester CH₃), 2.12 (3 H, s, OAc), 2.04 (9 H, 2s, 3xOAc),

m/z (C.I.) 317 (M⁺-OAc)

3. Synthesis of methyl (bromo-2,3,4-tri-*O*-acetylglucopyranosyl) uronate **48**

A solution of methyl 1,2,3,4-tetra-*O*-acetylglucopyranosyl uronate **56** (400mg, 1.06mmol) in 30% hydrogen bromide in acetic acid (4ml) was made up (some time and

shaking required for dissolution) and stored at 4°C for 20 hours. T.l.c. analysis indicated complete conversion. The solution was concentrated *in vacuo* and diluted with chloroform (10ml), washed with ice-water which was subsequently extracted with chloroform, and the combined chloroform extracts were dried over sodium sulfate, concentrated *in vacuo* and crystallised from absolute ethanol (2ml) at 4°C gave colourless prisms which were collected by filtration and washed with petroleum ether (350mg, 83%).

R_F: 0.35 (mobile phase = chloroform);

δ_H 6.65 (1 H, d, *J* 4.0, C¹-H), 5.62 (1 H, t, *J* 9.7, C³-H), 5.24 (1 H, dd, *J*_{4,5} 10.3, *J*_{4,3} 9.5, C⁴-H), 4.85 (1 H, dd, *J*_{2,3} 9.9, *J*_{2,1} 4.0, C²-H), 4.58 (1 H, d, *J* 10.4, C⁵-H), 3.77 (3 H, s, ester CH₃), 2.06-2.11 (9 H, 3s, 3xOAc).

4. Synthesis of methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate 58

A solution of methyl (bromo-2,3,4-tri-*O*-acetylglucopyranosyl) uronate **48** (5.8g, 15mmol), silver carbonate (2.0g, 1.4 eq) and water (0.12ml, 1.0 eq) in dry acetone (15ml) was made up and stirred for 12 hours. T.l.c. analysis (mobile phase = chloroform) indicated complete conversion. The solution was filtered washing 4 times with acetone, and the combined filtrate and washings were concentrated and dried *in vacuo* to a colourless syrupy solid (4.3g, 88%).

R_F: 0.3 (mobile phase = 40% ethyl acetate/petroleum ether);

δ_{H} 5.59 (1 H, t, J 9.7, C³-H), 5.55 (1 H, t, $J_{1,2;1,\text{OH}}$ 3.0, C¹-H), 5.19 (1 H, t, J 10.1, C⁴-H), 4.91 (1 H, dd, $J_{2,3}$ 10.0, $J_{2,1}$ 3.0, C²-H), 4.59 (1 H, d, J 10.1, C⁵-H), 3.82 (1 H, d(brd), J 3.0, OH), 3.75 (3 H, s, ester CH₃), 2.04-2.09 (9 H, 3s, 3xOAc).

5. Synthesis of 3-^tbutyldimethylsilylmorphine 57

Morphine (1.42g, 5.0mmol) was dissolved in a solution of sodium (130mg, 1.1 eq) in absolute ethanol (40ml). The solvent was evaporated *in vacuo* with trace amounts removed by forming an azeotrope with chloroform (4x), leaving the rapidly formed sodium morphinate. This was dissolved in THF (40ml) followed by slow addition of ^tbutyldimethylsilyl chloride (1.1g, 7.3mmol) and the solution was stirred for 12 hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated complete conversion. The solution was concentrated *in vacuo*, dissolved in chloroform, washed with water, dried over sodium sulfate, concentrated *in vacuo*, and crystallised from ethyl acetate (1.88g, 94%).

R_F: 0.4 (mobile phase = 10% methanol/chloroform);

δ_{H} 6.61 (1 H, d, J 8.1, C²-H), 6.51 (1 H, d, J 8.3, C¹-H), 5.71 (1 H, d-m, $J_{7,8}$ 9.9, C⁷-H), 5.26 (1 H, dm, $J_{8,7}$ 9.9, C⁸-H), 4.89 (1 H, dd, $J_{5,6}$ 6.6, $J_{5,7}$ 1.1, C⁵-H), 4.19 (1 H, s(brd), C⁶-H), 3.54 (1 H, s(brd), C⁹-H), 3.05 (1 H, d, $J_{\beta:\alpha}$ 19.0, C¹⁰-H _{β}), 2.96 (1 H, s(brd), OH), 2.81 (1 H, dd(brd), J_{gem} 13.0, $J_{16,15}$ C¹⁶-H_{eq}), 2.59 (3 H, s, N-CH₃), 2.5-2.7 (2 H, m, C¹⁴-H, C¹⁶-H_{ax}), 2.48 (1 H, dd, J_{gem} 19.0, $J_{10,9}$ 6.0, C¹⁰-H _{α}), 2.29 (1 H, td,

$J_{\text{gem}; 15,16}$ 13.0, $J_{15,16}$ 4.5, $\text{C}^{15}\text{-H}_{\text{ax}}$), 1.90 (1 H, dd, J_{gem} 13.0, $J_{15,16}$ 3.0, $\text{C}^{15}\text{-H}_{\text{eq}}$), 0.99 (9 H, s, 'BuSi), 0.20 (3 H, s, CH_3Si), 0.16 (3 H, s, CH_3Si);

m/z (EI; 70 eV) 399 (M^+), 342 ($\text{M}^+ - \text{'Bu}$).

6. Attempted synthesis of 3- $\text{'butyldimethylsilylmorphine-6-(methyl glucopyranosyl uronate)}$

A solution (A) of 3- $\text{'butyldimethylsilylmorphine}$ **57** (400mg, 1.0mmol) in THF (10ml) was made up with sonification. Meanwhile, a solution of triphenylphosphine (520mg, 2 eq) and methyl glucopyranosyl uronate **55** (310mg, 1.5 eq) in THF (10ml) was made up and diethylazodicarboxylate (DEAD) (0.3ml, 1.7 eq) was added dropwise. The solution was stirred for 15 minutes before solution (A) was added dropwise and the reaction mixture was stirred for 48 hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no conversion with both starting materials (**57**, R_F = 0.35; **55**, R_F = 0.5) remaining present although a new compound was indicated (R_F = 0.8). The mixture was evaporated to dryness *in vacuo* and flash chromatographed (mobile phase = 0-10% gradient methanol/chloroform) to afford the new compound as a brown oil (380mg). Compound was shown to be a complex of DEAD and triphenylphosphine.

δ_{H} 7.6 (15 H, m, PPh_3), 6.67 (1 H, s(brd), NH), 4.19 (4 H, q, J 7.2, CO_2Et), 1.26 (6 H, t, J 7.2, CO_2Et);

7. Attempted synthesis of 3-'butyldimethylsilylmorphine-6-[methyl (2,3,4-tri-*O*-acetylglucopyranosyl) uronate] using the Mitsunobu technique

i) A solution of 3-'butyldimethylsilylmorphine **57** (400mg, 1.0mmol), methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (500mg, 1.5 eq) and triphenylphosphine (520mg, 2 eq) in THF (10ml) was made up and DEAD (0.3ml, 1.7 eq) was added dropwise at 20°C. The solution was stirred for 2 hours before t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated the presence of starting material **57** and at least 6 other compounds.

ii) A solution (A) of 3-'butyldimethylsilylmorphine **57** (200mg, 0.5mmol) in THF (5ml) was made up with sonification. Meanwhile, a solution of triphenylphosphine (260mg, 2 eq) and mercuric bromide (310mg, 1.7 eq) in THF (3ml) was made up and DEAD (0.5ml, 5 eq) was added dropwise. The solution was stirred for 10 minutes before a solution of methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (250mg, 1.5 eq) in THF (3ml) was added dropwise and stirred was continued for a further 15 minutes. Solution (A) was added dropwise and the reaction mixture was stirred for 2 hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no conversion with both starting materials (**58**, $R_F = 0.8$) remaining present.

8. Attempted synthesis of methyl cyclohexyl-2,3,4-tri-*O*-acetylglucopyranosyl uronate

i) A solution (A) of cyclohexanol **59** (95mg, 0.95mmol) in THF (18ml) was made up. Meanwhile, a solution of triphenylphosphine (350mg, 1.6 eq) and methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (334mg, 1.05 eq) in THF (10ml) was made up and DEAD (0.18ml, 1.25 eq) was added dropwise. The solution was stirred for 15 minutes before solution (A) was added dropwise. T.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated no conversion with both starting materials (**59**, $R_F = 0.9$; **58**, $R_F = 0.5$) remaining present.

ii) A solution (A) of cyclohexanol **59** (85mg, 0.85mmol) in THF (16ml) was made up. Meanwhile, a solution of triphenylphosphine (320mg, 1.6 eq), mercuric bromide (380mg, 1.25 eq) and methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (300mg, 1.05 eq) in THF (9ml) was made up and DEAD (0.16ml, 1.25 eq) was added dropwise. The solution was stirred for 15 minutes before solution (A) was added dropwise. T.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated no conversion with both starting materials (**59**, $R_F = 0.9$; **58**, $R_F = 0.5$) remaining present.

iii) A solution (A) of cyclohexanol **59** (110mg, 1.1mmol) in THF (10ml) was made up. Meanwhile, a solution of methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (334mg,

1.05 eq) in THF (10ml) was made up and tributylphosphine (0.37ml, 1.6 eq) was added. The solution was cooled to -78°C and DEAD (0.18ml, 1.25 eq) was added dropwise. The solution was stirred for 10 minutes at 0°C before cooling again to -78°C and solution (A) was added dropwise. The solution was allowed slowly to warm to -5°C when a red colouration was noted. Reaction was continued at -5°C for 3 hours after which time t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated the presence of starting material **58** and a new compound which was shown to be the hydrazine reduction product of DEAD.

δ_{H} 6.70 (2 H, s(brd), 2xNH), 4.20 (4 H, q, J 7.2, CO₂Et), 1.28 (6 H, t, J 7.2, CO₂Et);

iv) A solution (A) of cyclohexanol **59** (110mg, 1.1mmol) in THF (10ml) was made up. Meanwhile, a solution of methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (334mg, 1.05 eq) and mercuric bromide (420mg, 1.25 eq) in THF (10ml) was made up and tributylphosphine (0.37ml, 1.6 eq) was added. The solution was cooled to -78°C and DEAD (0.18ml, 1.25 eq) was added dropwise. The solution was stirred for 10 minutes at 0°C before cooling again to -78°C and solution (A) was added dropwise. The solution was allowed slowly to warm to 20°C; no red colouration was noted. Reaction was continued at 20°C for 3 hours after which time t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated the presence of starting materials **58**, **59** and DEAD.

v) A solution (A) of cyclohexanol **59** (110mg, 1.1mmol) in acetonitrile (10ml) was made up. Meanwhile, a solution of methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (334mg, 1.05 eq) in acetonitrile (10ml) was made up and tributylphosphine (0.37ml, 1.6 eq) was added. The solution was cooled to -78°C and DEAD (0.18ml, 1.25 eq) was added dropwise. The solution was stirred for 10 minutes at 0°C when a red colouration was noted, before cooling to -78°C and solution (A) was added dropwise. The solution was allowed slowly to warm to 20°C and stirred for 3 hours after which time t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated the presence of starting material **58** and a new compound which was consistent with the hydrazine reduction product of DEAD.

δ_{H} consistent with iii).

9. Attempted synthesis of 3-'butyldimethylsilylmorphine-6-[methyl (2,3,4-tri-*O*-acetylglucopyranosyl) uronate]

i) A solution of methyl 1,2,3,4-tetra-*O*-acetylglucopyranosyl uronate **56** (376mg, 1mmol) and 3-'butyldimethylsilylmorphine **57** (420mg, 1.05 eq) in chloroform (0.5ml) was made up and cooled to 0°C. Boron trifluoride etherate (170mg, 0.15ml, 1.2 eq) was added dropwise and the solution was stirred at 20°C for 18 hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no conversion with both starting materials (**56**, R_{F} = 0.9) remaining present.

ii) A solution of methyl 1,2,3,4-tetra-*O*-acetylglucopyranosyl uronate **56** (376mg, 1mmol) and 3-*t*-butyldimethylsilylmorphine **57** (420mg, 1.05 eq) in chloroform (0.5ml) was made up and cooled to 0°C. Boron trifluoride etherate (380mg, 0.33ml, 2.7 eq) was added dropwise and the solution was stirred at 20°C for 18 hours. T.l.c. analysis (mobile phase = 25% methanol/chloroform) indicated conversion to a new compound ($R_F = 0.35$). Water (5ml) was added and the new compound was extracted into chloroform (5ml). Separation and evaporation *in vacuo* gave the product as an off-white solid (210mg). Compound was consistent with morphine.

10. Attempted synthesis of methyl (ethyl-1-phenylpropenoate)-2,3,4-tri-*O*-acetylglucopyranosyl uronate **63**

A solution of methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (334mg, 1.0mmol) and sodium hydride (26mg, 1.1 eq) in THF (10ml) was made up and stirred for 30 minutes. Ethyl phenyl propiolate (0.2ml, 1.2 eq) was added dropwise and the reaction mixture was maintained at 50°C. T.l.c. analysis (mobile phase = 20% methanol/chloroform) indicated no conversion with both starting materials remaining present.

11. Attempted synthesis of methyl pyrimidyl-2,3,4-tri-*O*-acetylglucopyranosyl uronate **64**

A solution of methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (334mg, 1.0mmol) and sodium hydride (26mg, 1.1 eq) in THF (10ml) was made up and stirred for 30 minutes. A solution of 2-chloropyrimidine (140mg, 1.2 eq) in THF (5ml) was added dropwise and the reaction mixture was maintained at 50°C. T.l.c. analysis (mobile phase = 20% methanol/chloroform) indicated no conversion with both starting materials (**58**, R_F = 0.9) remaining present.

12. Attempted synthesis of methyl (2-pyridinecarboxylate)-2,3,4-tri-*O*-acetylglucopyranosyl uronate **65**

A solution of methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (668mg, 2.0mmol) and triethylamine (0.3ml, 2.2 eq) in DCM (10ml) was made up and a solution of picolinoyl chloride (prepared as described¹³¹) (312mg, 1.1 eq) in DCM (10ml) was added. After stirring at 50°C for 24 hours, t.l.c. analysis (mobile phase = 20% methanol/chloroform) indicated no conversion with both starting materials remaining present.

13. Synthesis of methyl 2,3,4-tri-*O*-acetyl-6-triphenylmethylglucopyranoside

A solution of methyl α -D-glucopyranoside **68** (10.0g, 52mmol) and triphenylmethyl chloride (14g, 1.0 eq) in pyridine (80ml) was stirred until complete dissolution (24 hours) was achieved. Acetic anhydride (40ml, 420mmol) was added and the solution was stirred for a further 5 hours. The solution was poured onto ice-water (200ml) and the resulting colourless precipitate was collected by filtration, washed with water and recrystallised from ethanol (19.1g, 65%).

m.p. 130-134°C;

δ_{H} 7.42 (6 H, m, CPh₃), 7.42 (9 H, m, CPh₃), 5.42 (1 H, t, J 10.0, C⁴-H), 5.06 (1 H, t, J 10.0, C³-H), 5.01 (1 H, d, J 3.8, C¹-H), 4.92 (1 H, dd, $J_{2,3}$ 10.0, $J_{2,1}$ 3.8, C²-H), 3.90 (1 H, ddd, $J_{5,4}$ 10.0, $J_{5,6}$ 5.0, $J_{5,6}$ 2.5, C⁴-H), 3.46 (3 H, s, OMe), 3.18 (1 H, dd, J_{gem} 10.5, $J_{6,5}$ 2.5, C⁶-H), 3.10 (1 H, dd, J_{gem} 10.5, $J_{6,5}$ 5.0, C⁶-H), 2.08 (3 H, s, OAc), 1.98 (3 H, s, OAc), 1.72 (3 H, s, OAc).

14. Synthesis of methyl 2,3,4-tri-*O*-benzyl-6-triphenylmethylglucopyranoside

A solution of methyl 2,3,4-tri-*O*-acetyl-6-triphenylmethylglucopyranoside (8.7g, 15mmol) and sodium (35mg, 0.1 eq) in methanol (100ml) was made up and stirred for 5 hours. T.l.c. analysis (mobile phase = ethyl acetate) indicated complete conversion so the solution was concentrated *in vacuo* to an oil. DME (100ml) was added,

followed by sodium hydride (2.7g, 6.5 eq) portionwise with stirring. Benzyl bromide (15ml, 9 eq) was added and the solution was boiled for 8 hours. T.l.c. analysis (mobile phase = 10% ethyl acetate/petroleum ether) indicated complete conversion, plus benzyl by-product. The solution was quenched with methanol with stirring for 15 minutes, and concentrated *in vacuo* to a brown oil. Benzyl by-products were removed by distillation (100°C, 1.5mbar) to afford a brown syrup (5.5g, 52%).

R_F 0.2 (mobile phase = 10% ethyl acetate/petroleum).

15. Synthesis of methyl 2,3,4-tri-*O*-benzylglucopyranoside

A solution of methyl 2,3,4-tri-*O*-benzyl-6-triphenylmethylglucopyranoside (5.5g, 7.4mmol) in glacial acetic acid (40ml) was cooled to 5°C and 45% hydrobromic acid in acetic acid (1.33ml, 1.0 eq) was added. The solution was stirred for 30 seconds and filtered. The filtrate was quenched with water (100ml) and extracted into chloroform which was neutralised with saturated sodium hydrogen carbonate, dried over sodium sulfate, and concentrated *in vacuo* to a brown oil which was flash chromatographed (mobile phase = 20-60% gradient ethyl acetate/petroleum ether) to afford a colourless oil (1.5g, 44%).

R_F 0.1 (mobile phase = 40% ethyl acetate/petroleum).

16. Synthesis of methyl (methyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate 70

A solution of methyl 2,3,4-tri-*O*-benzylglucopyranoside (1.5g, 3.2mmol) in acetone (24ml) was cooled to 5°C and a solution of chromium trioxide (0.87g, 8.7mmol) in 3.5M sulfuric acid (4ml) was added with stirring. After 10 minutes, the solution was stirred at 20°C for exactly 60 minutes, filtered (washing with acetone until washings were colourless) and the combined filtrate and washings were quenched with crushed ice. The organic solvent was evaporated *in vacuo* and the resulting aqueous solution was extracted with chloroform which was washed with water, dried over sodium sulfate, and concentrated *in vacuo*, to a yellow oil. This was dissolved in methanol and loaded onto a column of Amberlite IRA-400(OH) ion-exchange resin (4.6ml) and eluted with acetic acid/methanol/water (45:45:10), concentrating to afford a yellow oil (1.7g). This was treated with excess diazomethane in ether for 10 minutes and quenched with acetic acid. Evaporation of the solvents *in vacuo* gave a yellow oil >95% pure (1.6g, 100%!). The oil was flash chromatographed (mobile phase = 10-17% gradient ethyl acetate/petroleum ether) to afford an oil (0.7g, 44%).

R_F: 0.6 (mobile phase = 40% ethyl acetate/petroleum ether);

λ_{max} 2900 (s, arom C-H), 1750 (s, ester C=O);

δ_{H} 7.20-7.37 (15 H, m, 3x Bn), 4.91 (1 H, d, J_{gem} 10.8, Ph-CH₂), 4.83 (1 H, d, J_{gem} 10.8, Ph-CH₂), 4.82 (1 H, d, J_{gem} 12.1, Ph-CH₂), 4.79 (1 H, d, J_{gem} 10.8, Ph-CH₂), 4.64 (1 H, d, J_{gem} 12.1, Ph-CH₂), 4.59 (1 H, d, J 3.0, C¹-H), 4.57 (1 H, d, J_{gem} 10.5, Ph-CH₂), 4.19 (1 H, d, J 9.9, C⁵-H), 3.98 (1 H, t, J 9.3, C³-H), 3.72 (1 H, dd, $J_{4,3}$ 9.0,

$J_{4,5}$ 9.9, C⁴-H), 3.71 (3 H, s, ester CH₃), 3.57 (1 H, dd, $J_{2,3}$ 9.5, $J_{2,1}$ 3.5, C²-H), 3.40 (3 H, s, ether OCH₃);

(Found: C, 71.1; H, 6.60. C₂₉H₃₂O₇ requires C, 70.7; H, 6.55).

17. Attempted synthesis of methyl 2,3,4-tri-*O*-benzylglucopyranosyl uronate **69**

i) A solution of methyl (methyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate **70** (600mg, 1.2mmol) in glacial acetic acid (6ml) and acetic anhydride (1.1ml) was made up and stirred at 20°C. After 16 hours, t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated no reaction. The reaction was boiled for 8 hours, but t.l.c. analysis again showed no conversion. The mixture was concentrated *in vacuo* and ¹H n.m.r. confirmed the presence only of starting material.

ii) A solution of methyl (methyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate **70** (600mg, 1.2mmol) in glacial acetic acid (6ml) and acetic anhydride (1.1ml) was made up and stirred at 5°C and concentrated sulfuric acid (0.07ml, 1.1 eq) in glacial acetic acid (1ml) was added dropwise. The reaction was warmed and maintained at 40°C for 24 hours. T.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated no reaction. The temperature was raised to 60°C and after 12 hours the solution became dark while t.l.c. analysis indicated complete conversion to material running at the baseline. The reaction mixture was neutralised with saturated sodium hydrogen

carbonate, extracted into DCM (2x50ml), washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo* to a crude oil. A solution of this oil and sodium (6mg, 0.2 eq) in methanol (12.5ml) was stirred for 10 hours. T.l.c. analysis (mobile phase = 20% ethyl acetate/petroleum ether) indicated the presence of at least 6 compounds.

iii) A solution of methyl (methyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate **70** (500mg, 1.0mmol) in iodotrimethylsilane (0.5ml, 3.5 eq) was made up and stirred at 20°C. After 16 hours, the solution was quenched with water and extracted into chloroform. However, t.l.c. analysis (mobile phase = 2% acetone/DCM) indicated complete conversion to material which was not eluted from the baseline, compared with a standard of target compound which ran with $R_F = 0.3$.

iv) A solution of methyl (methyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate **70** (500mg, 1.0mmol) in iodotrimethylsilane (0.16ml, 1.1 eq) was made up and stirred at 20°C. After 16 hours, the solution was quenched with water and extracted into chloroform. T.l.c. analysis (mobile phase = 2% acetone/DCM) indicated complete conversion to material which was not eluted from the baseline (see above).

v) A solution of methyl (methyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate **70** (100mg, 0.2mmol) in boron tribromide (0.3ml, 1.5 eq) was made up and stirred at 16°C. After

1 hour, t.l.c. analysis (mobile phase = 10% ethyl acetate/petroleum ether) indicated complete conversion to material with $R_F = 0.3$. The reaction was quenched with saturated sodium hydrogen carbonate (5ml) and the product was extracted into ether (5ml). T.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) now showed only a new product which was not eluted from the baseline, compared with a standard of target compound which was eluted with $R_F = 0.4$.

18. Attempted synthesis of methyl 1,2,3,4-tetra-*O*-benzylglucopyranosyl uronate

i) A solution of methyl glucopyranosyl uronate **55** (7.0g, 33.7mmol) in DME (100ml) was made up with stirring, and added to which were benzyl bromide (5.0g, 3.5ml, 8 eq) and sodium hydride (6.0g, 8 eq). The solution was boiled for 3 days but t.l.c. analysis (mobile phase = ethyl acetate) indicated no conversion. Tetrabutylammonium iodide (2.5g, 0.2 eq) was added and the reaction was continued for 24 hours, but t.l.c. analysis again showed no conversion.

ii) A solution of methyl glucopyranosyl uronate **55** (5.9g, 27mmol) in DMF (80ml) was made up with stirring, and added to which were benzyl bromide (0.75ml, 1.1 eq) and sodium hydride (0.62g, 1.1 eq). The solution was heated to 100°C for 10 hours after which, t.l.c. analysis (mobile phase = ethyl acetate) indicated no conversion. Further

portions (1.1 eq) of sodium hydride and benzyl bromide were added and the reaction was continued for 12 hours. Again, t.l.c. analysis suggested no conversion.

iii) A solution of methyl glucopyranosyl uronate **55** (1.2g, 5.5mmol) and benzyl trichloroacetimidate (7.3g, 6 eq) in DCM (10ml) was made up, and boron trifluoride etherate (470mg, 0.4ml, 0.6 eq) was added dropwise. The solution was stirred for 16 hours after which time, a yellow precipitate had formed. The reaction was quenched with saturated sodium hydrogen carbonate and extracted into ethyl acetate (precipitate dissolved when ethyl acetate was added). T.l.c. analysis (mobile phase = ethyl acetate) indicated no conversion.

19. Synthesis of methyl 'butyldimethylsilyl-2,3,4-tri-*O*-acetylglucopyranosyl uronate **74**

A solution of methyl 2,3,4-tri-*O*-acetylglucopyranosyl uronate **58** (6.26g, 18.7mmol), imidazole (3.75g, 3 eq), and 'butyldimethylsilyl chloride (3.1g, 1.1 eq) in THF (100ml) was made up and stirred at 20°C. After 1 hour, t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated partial conversion with complete conversion after 2 days. 1M hydrochloric acid (200ml) was added and the product was extracted into ethyl acetate (4x100ml), dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo* to afford a colourless crystalline solid (7.8g, 92%).

R_F 0.8 (mobile phase = 40% ethyl acetate/petroleum ether);

δ_H 5.26 (1 H, t, $J_{1,2;1,4}$ 6.9, C¹-H), 5.24 (1 H, t, $J_{3,4;3,2}$ 6.9, C³-H), 4.97 (1 H, dq, $J_{4,2}$ 9.5, $J_{4,5;4,3;4,1}$ 7.0, C⁴-H), 4.79 (1 H, d, $J_{5,4}$ 7.5, C⁵-H), 4.03 (1 H, dt, $J_{2,4}$ 9.7, $J_{2,1;2,3}$ 6.9, C²-H), 3.75 (3 H, s, CO₂Me), 2.03 (3 H, s, OAc), 2.02 (6 H, s, OAc), 0.87 (9 H, s, ^tBu), 0.14 (3 H, s, SiMe), 0.11 (3 H, s, SiMe);

δ_C 170.2 (Ac), 169.3 (Ac), 169.0 (Ac), 167.1 (CO₂Me), 95.8 (1), 73.0 (5), 72.5 (3), 72.1 (2), 69.5 (4), 52.8 (CO₂Me), 25.4 (CMe₃), 20.6 (Me), 20.5 (Me), 17.8 (C(CH₃)₃);

m/z (FAB) 447 (M⁺-H), 391 (M⁺-^tBu);

(Found: C, 50.9; H, 7.24. C₁₉H₃₂O₁₀Si requires C, 50.9; H, 7.20%).

20. Synthesis of methyl ^tbutyldimethylsilylglucopyranosyl uronate **75**

i) Methyl ^tbutyldimethylsilyl-2,3,4-tri-O-acetylglucopyranosyl uronate **74** (224mg, 0.5mmol) was dissolved in a solution of sodium methoxide in methanol, 0.5mg/ml, (4ml) and left to stand for 3 days. T.l.c. analysis (mobile phase = ethyl acetate) indicated partial (~50%) conversion with no further conversion after another 24 hours. The mixture was stood in a sonic bath for 2 days but this gave no further conversion. The solution was evaporated to dryness *in vacuo* to an oil which was flash chromatographed (mobile phase = 30-80% gradient ethyl acetate/petroleum ether) to

afford a colourless crystalline solid (53mg, 33%) plus starting material (4mg, 2%) and inseparable impurities (21mg). N.m.r revealed product as a 1:1 β : α anomeric mixture.

R_F 0.65 (mobile phase = ethyl acetate);

δ_H 5.26 (0.5 H, d, J 3.5, C^1 -H $_{\beta}$ (α -anomer)), 4.80 (0.5 H, s(brd), OH), 4.55 (0.5 H, d, J 7.3, C^1 -H $_{\alpha}$ (β -anomer)), 4.40 (0.5 H, s(brd), OH), 4.23 (0.5 H, d, J 9.0, C^5 -H (1 anomer)), 3.80 (1.5 H, s, CO₂Me (1 anomer)), 3.79 (1.5 H, s, CO₂Me (1 anomer)), 3.5-3.88 (4 H, m, C^3 -H, C^4 -H, C^2 -H (α -anomer), C^5 -H (1 anomer), OH), 3.38 (0.5 H, dd, J 9.0, J 7.5, C^2 -H (β -anomer)), 2.95 (0.5 H, s(brd), OH), 2.70 (0.5 H, s(brd), OH), 0.92, 0.90 (9 H, 2s, ^tBu (2 anomers)), 0.15, 0.13 (6 H, 2s, SiMe₂);

m/z (FAB) 323 (M^+ +H), 265 (M^+ -^tBu);

(Found: C, 47.4; H, 8.17. C₁₃H₂₆O₇Si requires C, 48.4; H, 8.13%).

ii) A solution of methyl ^tbutyldimethylsilyl-2,3,4-tri-O-acetylglucopyranosyl uronate **74** (224mg, 0.5mmol) in methanol (5ml) was carefully added to a solution of potassium carbonate (700mg, 10 eq) in water (5ml) giving a colourless suspension. After 5 minutes with vigorous stirring, t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated complete conversion to material which was not eluted from the baseline. Acetic acid was added very slowly to excess and the solution was partitioned between water and ether. The ether layer was collected while the aqueous layer was further extracted with DCM. T.l.c. analysis of all 3 layers revealed starting material in the ether layer, very little in the DCM layer and material which ran

at the baseline remaining in the aqueous layer. The ether layer was evaporated to dryness *in vacuo* to afford starting material as a colourless crystalline solid (220mg, 98%).

iii) A solution of methyl 'butyldimethylsilyl-2,3,4-tri-O-acetylglucopyranosyl uronate **74** (224mg, 0.5mmol) in methanol (9ml) was carefully added to a solution of potassium carbonate (700mg, 10 eq) in water (1ml) giving a colourless suspension. After 1 hour with vigorous stirring, t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated complete conversion to material which was not eluted from the baseline. Acetic acid was added very slowly to excess and the solution was partitioned between water and ether. T.l.c. analysis of both layers revealed only material which was not eluted from the baseline, present in the aqueous layer only. This could not be extracted into DCM either.

iv) A solution of methyl 'butyldimethylsilyl-2,3,4-tri-O-acetylglucopyranosyl uronate **74** (3.5g, 7.8mmol) and triethylamine (4g, 5.6ml, 5 eq) in methanol (100ml) was made up and stirred at 20°C. After 2 hours, t.l.c. analysis (mobile phase = ethyl acetate) indicated initial conversion to an intermediate with higher R_F than the desired product, plus a small amount of desired product. After 2 days, t.l.c. analysis revealed the product spot to be much more prominent with very little starting material remaining, and the conversion had not increased after a further 24 hours. The solution was evaporated to dryness *in vacuo* to an oil which was flash chromatographed (mobile

phase = 50-64% gradient ethyl acetate/petroleum ether) to afford desired product as an off-white solid (1.7g, 68%), starting material as a colourless crystalline solid (830mg, 24%) and a mixture of by-products (637mg). The new product was shown by n.m.r. to be ~90% pure. Recrystallisation from hot isopropyl ether gave colourless prisms (834mg, 33%).

Data consistent with i).

v) A solution of methyl 'butyldimethylsilyl-2,3,4-tri-O-acetylglucopyranosyl uronate **74** (255mg, 0.57mmol) and 2N ammonia (2.0ml, 7 eq) in methanol (6ml) was made up and left to stand for 7 days. T.l.c. analysis (mobile phase = ethyl acetate) after 4 days indicated partial conversion to the desired product, plus a large amount of by-product with much lower R_F value, but after 7 days there was little starting material remaining. The solution was evaporated to dryness *in vacuo* to an oil which was taken up in water and extracted into ether, dried over sodium sulfate, and evaporated again to an oil. Crystallisation from hot isopropyl ether gave colourless prisms (45mg, 25%).

Data consistent with i).

21. Attempted synthesis of methyl 'butyldimethylsilyl-2,3,4-tri-O-
benzylglucopyranosyl uronate

i) A solution of methyl 'butyldimethylsilylglucopyranosyl uronate **75** (322mg, 1.0mmol) and benzyl trichloroacetimidate (880mg, 4 eq) in DCM (5ml) was made up and boron trifluoride etherate (0.05ml, 57mg, 0.4 eq) was added dropwise with stirring. After 1 hour, t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) showed conversion to at least 5 new compounds with no change after 17 hours. A further portion of 0.4 eq boron trifluoride etherate was added and the reaction was continued. After 2 hours, t.l.c. analysis showed even more spots than before and the reaction was abandoned.

ii) A solution of methyl 'butyldimethylsilylglucopyranosyl uronate **75** (161mg, 0.5mmol), benzyl bromide (300mg, 0.2ml, 3.5 eq) and sodium hydride (45mg, 3.5 eq) in DME (10ml) was made up and boiled for 24 hours. T.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) showed no conversion. A further portion of 4 eq sodium hydride was added and the reaction was continued. After 8 hours, t.l.c. analysis showed strong u.v. active spots eluted close to the solvent front consistent with expected benzyl by-products. A further portion of 2 eq benzyl bromide was also added and the reaction was continued for another 12 hours. T.l.c. analysis showed no change from previous.

iii) A solution of methyl 'butyldimethylsilylglucopyranosyl uronate **75** (72mg, 0.22mmol), benzyl bromide (382mg, 0.27ml, 10 eq) and sodium hydride (55mg, 10 eq) in DMF (3ml) was made up and stirred at 120°C for 24 hours. T.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) showed no conversion.

iv) A solution of methyl 'butyldimethylsilylglucopyranosyl uronate **75** (146, 0.45mmol), benzyl bromide (345mg, 0.24ml, 4.5 eq) and silver oxide (470mg, 4.5 eq) in DMF (10ml) was made up and stirred at 20°C for 4 days. T.l.c. analysis (mobile phase = 10% ethyl acetate/petroleum ether) showed no conversion. The solution was heated at 100°C and stirred for 12 hours. Again, t.l.c. analysis indicated no reaction. Further portions (10 eq) silver oxide and benzyl bromide were added and the temperature was raised to at 130°C. After 24 hours, t.l.c. analysis showed strong u.v. active spots eluted close to the solvent front consistent with expected benzyl by-products.

v) A solution of sodium hydride (60mg, 4.5 eq) in DMSO (1ml) was added dropwise to a solution of methyl 'butyldimethylsilylglucopyranosyl uronate **75** (187mg, 0.58mmol) in DMSO (1ml) and stirred for 1 hour. Benzyl chloride (664mg, 0.60ml, 9 eq) was added dropwise and the mixture was stirred at 20°C for 12 hours. T.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) showed no conversion. The temperature was raised to 120°C for 8 hours, but t.l.c. analysis showed no change.

22. Synthesis of allyl glucopyranoside 73

A suspension of α -D-glucose (80g, 0.44mol) in allyl alcohol (170g, 200ml) was stirred while dry hydrogen chloride gas was bubbled through until the mass had increased by 5g, 0.3 eq. The solution was stirred at 70°C for 7 hours when full dissolution was attained. After cooling, neutralisation with barium carbonate and filtration, the solvent was evaporated *in vacuo* leaving a brown syrup (120g) which was extracted with hot acetone (15x300ml) and concentrated *in vacuo* to a syrup. T.l.c. analysis (mobile phase = 33% toluene/acetone) showed starting material to still be present. An attempt at purifying by flash chromatography failed with all the material being recovered immediately. Recovery of syrup was 26g, 25% assuming 95% purity.

R_F 0.1 (mobile phase = 33% toluene/acetone).

23. Synthesis of allyl 6-triphenylmethylglucopyranoside

A solution of allyl glucopyranoside **75** (14.0g, 64mmol) and triphenylmethyl chloride (18g, 1.0 eq) in pyridine (120ml) was stirred, monitoring by t.l.c. analysis (mobile phase = 33% toluene/acetone). After 20 hours, t.l.c. analysis indicated almost complete conversion. The pyridine was evaporated *in vacuo* leaving an oil which was dissolved in ethyl acetate, washed with water, dried over sodium sulfate, concentrated

in vacuo and flash chromatographed (mobile phase = 30% ethyl acetate/petroleum ether) to afford a colourless solid (14g, 48%).

R_F 0.15 (mobile phase = 40% ethyl acetate/petroleum).

24. Synthesis of allyl 2,3,4-tri-*O*-benzyl-6-triphenylmethylglucopyranoside

A solution of allyl 6-triphenylmethylglucopyranoside (7.0g, 15mmol) in DME (100ml) was made up and sodium hydride (1.4g, 3.3 eq) was added portionwise with stirring. Benzyl bromide (6ml, 3.6 eq) was added and the solution was boiled for 5 hours. T.l.c. analysis (mobile phase = 10% ethyl acetate/petroleum ether) indicated complete conversion. The solution was filtered, and concentrated *in vacuo* to a brown oil. Flash chromatography gave a yellow syrup (8.9g, 80%).

R_F 0.25 (mobile phase = 10% ethyl acetate/petroleum).

25. Synthesis of allyl 2,3,4-tri-*O*-benzylglucopyranoside

A solution of allyl 2,3,4-tri-*O*-benzyl-6-triphenylmethylglucopyranoside (8.9g, 12mmol) and 1M hydrochloric acid (6ml, 6mmol) in acetone (54ml) was boiled for 2 hours. T.l.c. analysis (mobile phase = 20% ethyl acetate/petroleum ether) indicated complete conversion. The acetone was evaporated *in vacuo* and the resulting oil was

dissolved in *sec*-butanol, filtered and concentrated *in vacuo* to a brown oil which was flash chromatographed (mobile phase = 20% ethyl acetate/petroleum ether) to afford an oil (4.1g, 69%). ^1H n.m.r. indicates a 1:1 mixture of anomers.

R_F 0.25, 0.30 (mobile phase = 20% ethyl acetate/petroleum);

δ_H 7.35 (15 H, m, 3xOBn), 6.01 (1 H, m, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.30 (2 H, m, $\text{OCH}_2\text{CH}=\text{CH}_2$), 4.5-5.1 (8 H, m, 3x CH_2OPh , $\text{OCH}_2\text{CH}=\text{CH}_2$), 3.5-4.3 (7 H, m, $\text{C}^{1,2,3,4,5}\text{-H}$, 2x $\text{C}^6\text{-H}$), 1.80 (1 H, s(brd), OH).

26. Synthesis of methyl (allyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate

A solution of allyl 2,3,4-tri-*O*-benzylglucopyranoside (4.1g, 8.4mmol) in acetone (40ml) was cooled to -10°C and a solution of chromium trioxide (2.2g, 15mmol) in 3.5M sulfuric acid (9ml) was added with stirring. The solution was stirred at 20°C for exactly 3 hours before pouring onto crushed ice and extracting into DCM. This was dried over sodium sulfate, and concentrated *in vacuo*, to a yellow oil which was treated with excess diazomethane in ether for 10 minutes and quenched with acetic acid. Evaporation of the solvents *in vacuo* gave a yellow oil which was flash chromatographed (mobile phase = 10-17% gradient ethyl acetate/petroleum ether) to afford a clear oil (2.4g, 55%).

R_F 0.45 (mobile phase = 10% ethyl acetate/petroleum).

27. Synthesis of methyl 2,3,4-tri-*O*-benzylglucopyranosyl uronate **69**

A solution of methyl (allyl-2,3,4-tri-*O*-benzylglucopyranosyl) uronate (2.4g, 4.6mmol), hydrated sodium acetate (1.61g, 16mmol) and palladium chloride (970mg, 1.2 eq) in acetic acid (10ml) was stirred for 3 days, after which, t.l.c. analysis (mobile phase = 2% acetone/DCM) indicated complete conversion with a by-product. The solution was filtered, concentrated *in vacuo*, and flash chromatographed to afford a yellow crystalline solid (1.4g, 63%). ¹H n.m.r. indicates a 3:1 α:β mixture of anomers.

R_F 0.45 α, 0.65 β (mobile phase = 2% acetone/DCM);

m.p. 106-110°C, (lit. 110-112°C);

δ_H 7.3 (15 H, m, 3x Bn), 5.22 (0.75 H, d, *J* 3.5, C¹-H_β (α anomer)), 4.45-5.0 (7 H, m, 3xPh-CH₂, C⁵-H), 3.7-4.1 (2 H, m, C³-H, C⁴-H), 3.73 (0.25x3 H, s, ester CH₃ (β anomer)), 3.71 (0.75x3 H, s, ester CH₃ (α anomer)), 3.61 (0.75 H, dd, *J*_{2,3} 9.0, *J*_{2,1} 3.5, C²-H (α anomer), 3.46 (0.25 H, dd, *J*_{2,3} 9.5, *J*_{2,1} 8.5, C²-H (β anomer)).

28. Synthesis of methyl trichloroacetimidyl-2,3,4-tri-*O*-benzylglucopyranosyl uronate **66**

A solution of methyl 2,3,4-tri-*O*-benzylglucopyranosyl uronate **69** (1.15g, 2.4mmol), trichloroacetonitrile (2.4ml, 10 eq) and sodium hydride (67mg, 0.7 eq) in DCM (25ml)

was stirred for 15 minutes. T.l.c. analysis (mobile phase = 30% ethyl acetate/petroleum ether) indicated almost complete conversion. The mixture was concentrated *in vacuo*, and flash chromatographed to afford a colourless oil which crystallised overnight (1.05g, 70%) and starting material (170mg, 15%). ^1H n.m.r. indicates presence only of α anomer.

R_F 0.35 (mobile phase = 10% ethyl acetate/petroleum);

δ_H 8.65 (1 H, s, NH), 7.25 (15 H, m, 3x Bn), 6.50 (1 H, d, J 3.5, C¹-H), 4.96 (1 H, d, J 11.0, OCH₂Ph), 4.84 (1 H, d, J 11.0, OCH₂Ph), 4.82 (1 H, d, J 10.5, OCH₂Ph), 4.75 (1 H, d, J 11.0, OCH₂Ph), 4.70 (1 H, d, J 11.0, OCH₂Ph), 4.59 (1 H, d, J 11.0, OCH₂Ph), 4.42 (1 H, d, J 10.0, C⁵-H), 4.06 (1 H, t, J 9.5, C³-H), 3.70 (3 H, s, CO₂Me), 3.7-3.9 (2 H, m, C²-H, C⁴-H).

29. Attempted synthesis of codeine-6-methyl 2,3,4-tri-*O*-benzylglucopyranosyl uronate

A solution of codeine (197mg, 0.66mmol) and methyl trichloroacetimidyl-2,3,4-tri-*O*-benzylglucopyranosyl uronate **66** (490mg, 1.2 eq) in DCM (10ml) was made up and boron trifluoride etherate (0.1ml, 0.88mmol) was added dropwise with stirring. After 3 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction of codeine although starting glycoside **66** was converted to methyl 2,3,4-tri-*O*-benzylglucopyranosyl uronate **69**.

30. Attempted synthesis of 3-'butyldimethylsilylmorphine-6-methyl 2,3,4-tri-*O*-benzylglucopyranosyl uronate

A solution of 3-'butyldimethylsilylmorphine **57** (100mg, 0.25mmol) and methyl trichloroacetimidyl-2,3,4-tri-*O*-benzylglucopyranosyl uronate **66** (187mg, 1.2 eq) in DCM (1.8ml) was made up and boron trifluoride etherate (0.006ml, 0.2 eq) was added dropwise at -23°C with stirring. After 2 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction. A further portion of boron trifluoride etherate (0.03ml, 1.0 eq) was added and the reaction was continued for 1.5 hours. T.l.c. analysis indicated no reaction of 3-'butyldimethylsilylmorphine although starting glycoside **66** was converted to methyl 2,3,4-tri-*O*-benzylglucopyranosyl uronate **69**.

31. Synthesis of methyl cyclohexyl 2,3,4-tri-*O*-benzylglucopyranosyl uronate **76**

A solution of cyclohexanol (25mg, 0.25mmol) and methyl trichloroacetimidyl-2,3,4-tri-*O*-benzylglucopyranosyl uronate **66** (187mg, 1.2 eq) in DCM (1.8ml) was made up and boron trifluoride etherate (0.006ml, 0.2 eq) was added dropwise at -23°C with stirring. After 2 hours, t.l.c. analysis (mobile phase = 10% ethyl acetate/petroleum ether) showed the reaction to have formed a complex mixture. The solution was quenched with sodium hydrogen carbonate and extracted into DCM, dried over sodium sulfate, and evaporated to dryness *in vacuo* to an oil which was flash chromatographed (mobile phase = 10% ethyl acetate/petroleum ether). This gave product (22mg, 16%) which was further purified by t.l.c.* (16mg, 12%), and the glycoside by-product (88mg, 61%).

Product was a mixture of anomers α : β 69:31;

*elemental analysis suggests 8% silica impurity from preparative t.l.c. purification.

R_F 0.45 (mobile phase = 10% ethyl acetate/petroleum);

δ_H 7.36-7.20 (15 H, m, 3x Ph), 5.00-4.55 (6.7 H, m, 3x CH_2Ph + C^1-H_β (α anomer)), 4.33 (0.31 H, d, J 9.9Hz, C^1-H_α (β anomer)), 3.45-4.05 (4 H, m, C^2-H , C^3-H , C^4-H , C^5-H), 3.72 (3 H, 2s, CO_2CH_3 (2 anomers)), 1.20-2.00 (11 H, m, 1-*O*-cyclohexyl).

m/z (FAB) 561 ($M^+ + H$) 560 (M^+), 559 ($M^+ - H$);

(Found: C, 67.3; H, 6.61. $C_{34}H_{40}O_7$ requires C, 72.8; H, 7.20. With 8% silica impurity, requires C, 67.3; H, 6.65).

32. Attempted synthesis of codeine-6-methyl 2,3,4-tri-*O*-benzylglucopyranosyl uronate

A solution of codeine (165mg, 0.55mmol) in THF (5ml) was stirred at 0°C and sodium hydride (14mg, 1.05 eq) was carefully added and the solution was stirred for 1 hour. A solution of dibenzo-18-crown-6 (10mg) in benzene (20ml) was added and the solution was cooled to -15°C. A solution of methyl trichloroacetimidyl-2,3,4-tri-*O*-benzylglucopyranosyl uronate **66** (380mg, 1.1 eq) in benzene (10ml) was added dropwise followed by addition of boron trifluoride etherate (0.086ml, 1.2 eq) with stirring. After 3 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction of codeine or glycoside.

33. Synthesis of 6 β -chlorocodide 77

A solution of phosphorus pentachloride (2.25g, 10.8mmol) in chloroform (10ml) was made up at 0°C and codeine (2.0g, 6.7mmol) was added in portions. The solution was stirred at 20°C for 2 hours before ether (10ml) was added. The solvent (ether + chloroform) was decanted off and the golden residue was treated with saturated sodium carbonate giving a violet colour. The solution was gently heated until the colour disappeared and left to cool, allowing formation of brown crystals which were filtered off, washed with water and dried *in vacuo* (1.77g, 83%). Further purification by flash chromatography gave a light brown solid (1.59g, 75%).

R_F 0.7 (mobile phase = 10% methanol/chloroform);

$[\alpha]_D^{22}$ -341° (lit. -383°);

δ_H 6.64 (1 H, d, J 8.2, C²-H), 6.55 (1 H, d, J 8.2, C¹-H), 5.95 (1 H, ddd, $J_{7,8}$ 9.5, $J_{7,6}$ 6.0, $J_{7,14}$ 3.0, C⁷-H), 5.64 (1 H, dd, $J_{8,7}$ 9.5, $J_{8,14}$ 2.0, C⁸-H), 5.23 (1 H, s, C⁵-H), 4.66 (1 H, d, $J_{6,7}$ 6.0, C⁶-H), 3.84 (3 H, s, OMe), 3.31 (1 H, dd, $J_{9,10\alpha}$ 6.0, $J_{9,14}$ 3.5, C⁹-H), 3.06 (1 H, d, J_{gem} 15.8, C¹⁰-H $_{\beta}$), 2.60 (1 H, dd, J_{gem} 12.0, $J_{16,15}$ 5.0, C¹⁶-H $_{eq}$), 2.41 (3 H, s, NMe), 2.3-2.5 (3 H, m, C¹⁴-H, C¹⁶-H $_{ax}$, C¹⁰-H $_{\alpha}$), 1.89 (1 H, d(brd), J_{gem} 12.0, C¹⁵-H $_{eq}$).

34. Attempted synthesis of codeine-6-cyclohexylether

A solution of 6- β -chlorocodide **77** (318mg, 1.0mmol) in THF (5ml) was added dropwise to a solution of cyclohexanol (120mg, 1.2 eq) and sodium hydride (30mg, 1.2 eq) in THF (5ml) at 0°C and the solution was stirred at 20°C. After 2 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction.

35. Synthesis of methyl-2,3,4,6-tetra-*O*-benzylglucopyranoside

A solution of methyl α -D-glucopyranoside **68** (5.0g, 26mmol) and powdered potassium hydroxide (25g, 446mmol) in dioxane (15ml) was gently boiled while benzyl chloride (14.8g, 13.2ml, 4.4 eq) was added dropwise over 5 minutes and the solution was boiled for a further 1 hour. The solvent was removed *in vacuo* and the residue was taken up in water, extracted into ether, dried over sodium sulfate, and concentrated again *in vacuo* to an oil. Purification of the product by flash chromatography (mobile phase = 10% ethyl acetate/petroleum ether) gave a colourless solid (11.7g, 82%).

R_F 0.15 (mobile phase = 10% ethyl acetate/petroleum ether);

m.p. 154°C (lit. 151-152°C);

δ_{H} 7.2 (20 H, m, OBn), 5.00 (1 H, d, J 11.0, OBn), 4.4-4.9 (8 H, m, 7 H: OBn, + C¹-H), 4.00 (1 H, t, J 9.5, C³-H), 3.5-3.8 (4 H, m, C⁴-H, C⁵-H, 2x C⁶-H), 3.57 (1 H, dd, $J_{2,3}$ 9.0, $J_{2,1}$ 3.5, C²-H), 3.39 (3 H, s, OMe);

(Found: C, 74.6; H, 6.91. C₃₅H₃₈O₆ requires C, 75.8; H, 6.91).

36. Synthesis of 2,3,4,6-tetra-*O*-benzylglucopyranoside

A solution of methyl-2,3,4,6-tetra-*O*-benzylglucopyranoside (11.7g, 21mmol) in glacial acetic acid (150ml) at 100°C was diluted with boiling 2N hydrochloric acid (54ml, 5.0 eq). The solution was boiled for 2 hours before addition of a further portion of boiling 2N hydrochloric acid (5 eq) and further boiling for 24 hours. The mixture was poured into 1litre of water at left for 2 days. The resulting crystals were collected by filtration and recrystallised from isopropanol as a colourless solid (4.7g, 45%).

R_F 0.1 (mobile phase = 40% ethyl acetate/petroleum ether).

37. Synthesis of 1-*O*-(2-ethylcarboxylate-1-phenylethenyl)-2,3,4,6-tetra-*O*-benzylglucopyranoside 60

2,3,4,6-tetra-*O*-benzylglucopyranoside (1.08g, 2.0mmol) was added to a stirred suspension of sodium hydride (55mg, 1.1 eq) in THF (10ml) and stirring was

continued for 30 minutes. A solution of ethyl phenyl propiolate, (420mg, 0.4ml, 1.2 eq) in THF (5ml) was added and the solution was stirred at 50°C for 3 hours before quenching with methanol, concentrated *in vacuo* and flash chromatographed (mobile phase = 15% ethyl acetate/petroleum ether) giving the product as a brown oil (730mg, 51%). Mixture of 2 geometric alkenic isomers and 2 anomers.

T.l.c.: 4 spots. R_F 0.6, 0.65, 0.7, 0.75 (mobile phase = 30% ethyl acetate/petroleum ether)

38. Synthesis of 1-*O*-(2-pyrimidyl)-2,3,4,6-tetra-*O*-benzylglucose 61

2,3,4,6-tetra-*O*-benzylglucopyranoside (1.08g, 2.0mmol) was added to a stirred suspension of sodium hydride (55mg, 1.1 eq) in THF (10ml) and stirring was continued for 30 minutes. A solution of 2-chloropyrimidine, (275mg, 1.2 eq) in THF (5ml) was added and the solution was stirred at 50°C for 3 hours before quenching with methanol, concentrated *in vacuo* and flash chromatographed (mobile phase = 30% ethyl acetate/petroleum ether) giving the product as a yellow oil (700mg, 57%). Shown to be a 2:1 β : α mixture of anomers.

T.l.c.: 2 spots. R_F 0.6, 0.65 (mobile phase = 40% ethyl acetate/petroleum ether)

δ_H 8.50 (2 H, m, pyrim N-CH), 7.2 (20 H, m, OBn), 6.95 (1 H, m, pyrim C-CH), 6.67 (1 H, d, J 3.5, C¹-H (α anomer)), 6.02 (1 H, d, J 7.5, C¹-H (β anomer)), 4.2-5.05 (9 H, m, 4x OBn + C⁵-H), 3.6-3.9 (5 H, m, C²-H, C³-H, C⁴-H, 2x C⁶-H).

39. Attempted synthesis of codeine-6-(2,3,4,6-tetra-*O*-benzylglucopyranoside) **78**

A solution of 1-*O*-(2-ethylcarboxylate-1-phenylethenyl)-2,3,4,6-tetra-*O*-benzylglucopyranoside **60** (355mg, 0.5mmol) and codeine (165mg, 0.55mmol) in acetonitrile (5ml) was made up and stirred at -40°C. Trimethylsilyltriflate (122mg, 0.1ml, 0.55mmol) was added dropwise and stirring was continued at -40°C. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction. The solution was allowed slowly to warm to 20°C, monitoring by t.l.c. No change was observed.

40. Synthesis of codeine-6-(2,3,4,6-tetra-*O*-benzylglucopyranoside) **78**

A solution of 1-*O*-(2-pyrimidyl)-2,3,4,6-tetra-*O*-benzylglucopyranoside **61** (309mg, 0.5mmol) and codeine (165mg, 0.55mmol) in acetonitrile (5ml) was made up and stirred at -40°C. Trimethylsilyltriflate (122mg, 0.1ml, 0.55mmol) was added dropwise and stirring was continued at -40°C. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated virtually complete conversion after 3 hours. The solution was quenched with saturated sodium hydrogen carbonate, extracted into chloroform, and flash chromatographed (mobile phase = 5% methanol/chloroform) to afford a sticky colourless solid (140mg, 35%). Shown to be 1:1 α : β mixture of anomers.

R_F 0.7 (mobile phase = 10% methanol/chloroform);

δ_{H} 7.18-7.53 (20 H, m, 4x Ph), 6.65 (1 H, 2d, J 8.0, C²-H (2 anomers)), 6.56 (0.5 H, d, J 8.0, C¹-H (1 anomer)), 6.52 (0.5 H, d, J 8.0, C¹-H (1 anomer)), 5.92 (0.5 H, d, J 9.9, C⁷-H (1 anomer)), 5.83 (0.5 H, d, J 9.9, C⁷-H (1 anomer)), 5.30-5.40 (1.5 H, m + d, J 11.5, C⁸-H, OBn (1 anomer)), 4.40-5.05 (11 H, m, 7.5 H: CH₂Ph + C⁵-H, C¹-H, C³-H (1 anomer), C⁵-H), 4.10 (0.5 H, t, J 9.2, C³-H (1 anomer)), 4.00 (1 H, m, C⁶-H), 3.84 (1.5 H, s, OCH₃ (1 anomer)), 3.69 (1.5 H, s, OCH₃ (1 anomer)), 3.55-3.81 (4 H, C²-H, , C⁴-H, 2x C⁶-H), 3.41 (1 H, m, C⁹-H), 3.10 (1 H, 2d overlap, J 19, C¹⁰-H_β), 2.74 (0.5 H, m, C¹⁶-H_{eq}), 2.67 (0.5 H, m, C¹⁶-H_{eq}), 2.48 (3 H, 2s, NCH₃), 2.30-2.65 (3 H, m, C¹⁴-H, C¹⁶-H_{ax}, C¹⁰-H_α), 2.00-2.20 (1 H, 2s(brd), C¹⁵-H_{ax} (2 anomers)), 1.78-2.00 (1 H, 2m, C¹⁵-H_{eq});

δ_{C} 138.6 (4), 138.0 (3), 131.6 (7), 130.4 (12), 128.4 (8), 128.2 (Ph), 127.8 (Ph), 127.6 (Ph), 127.4 (Ph), 126.9, 126.6 (11, anomers), 118.7 (2), 114.8, 113.5 (1, anomers), 102.1, 98.7 (1, anomers), 91.3, 88.9 (5, anomers), 84.3, 81.7, 80.2, 77.6, 75.7, 74.8, 73.0 (5,3,2,4, anomers), 75.5 (CH₂Ph), 74.4 (CH₂Ph), 73.3 (2 CH₂Ph), 70.4 (6), 68.8 (6), 58.8 (OCH₃), 58.7 (9), 46.3 (16), 42.8 (NCH₃), 40.9, 40.7 (14, anomers), 35.5 (15), 20.5 (10);

m/z (FAB) 822 (M⁺+H), 821 (M⁺), 820 (M⁺-H), 730 (M⁺-CH₂Ph);

(Found C, 74.5%; H, 6.65%; N, 1.72%. C₅₂H₅₅O₈N requires C, 75.9%; H, 6.75%; N, 1.70%).

41. Attempted synthesis of 3-'butyldimethylsilylmorphine-6-(2,3,4,6-tetra-O-benzylglucopyranoside)

A solution of 1-*O*-(2-pyrimidyl)-2,3,4,6-tetra-*O*-benzylglucopyranoside **61** (660mg, 1.07mmol) and 3-'butyldimethylsilylmorphine **57** (480mg, 1.2mmol) in acetonitrile (15ml) was made up and stirred at -40°C. Trimethylsilyltriflate (288mg, 0.25ml, 1.3mmol) was added dropwise and stirring was continued at -40°C. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated virtually complete conversion after 3 hours. The solution was quenched with saturated sodium hydrogen carbonate, extracted into chloroform, and flash chromatographed (mobile phase = 5% methanol/chloroform) to afford a yellow oil which was shown to be morphine (310mg, 90%).

42. Attempted synthesis of codeine-6-(2,3,4,6-tetra-*O*-acetylglucopyranoside)

A solution of codeine (300mg, 1.0mmol) in benzene (15ml) was added to a boiling solution of silver carbonate (1.2g, 4.4 eq) and calcium sulfate (0.6g, 4.4 eq) in benzene (45ml). A solution of bromo-2,3,4,6-tetra-*O*-acetylglucopyranoside (1.2g, 3 eq) in benzene (45ml) was added dropwise to the boiling solution over 3 hours and the mixture was boiled using a Dean and Stark condenser. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction of codeine. The solvent was gradually removed by distilling off until ~10ml remained. The remaining solvent was

removed *in vacuo* and the residue was flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) returning codeine (170mg, 57%).

43. Attempted synthesis of codeine-6-glucoside

A solution of *o*-nitrophenyl glucopyranoside (75mg, 0.25mmol) and codeine (600mg, 8 eq) in phosphate buffer pH 5, 0.1M (0.8ml) was made up. The solution was shown to be at pH 8-9, so more dihydrogen phosphate plus a few drops of dilute hydrochloric acid were added until pH 5 was attained. β -glucosidase from almonds (250 units, 65mg) was added and the solution was maintained at 25°C for 24 hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated the presence of codeine and glucoside starting materials, plus a new compound ($R_F = 0.3$ c.f. codeine = 0.45). Evaporation *in vacuo* was followed by flash chromatography (mobile phase = 1.5-3% gradient methanol/chloroform) to afford the new product (100mg). Trituration with methanol gave a colourless crystalline solid (40mg). This was shown by n.m.r. to be a codeine-N salt, confirmed by basifying a small sample - t.l.c. analysis consistent with codeine.

44. Attempted synthesis of codeine-6-(2,3,4,6-tetra-*O*-acetylglucopyranoside) 82

A solution of codeine (150mg, 0.5mmol), bromo-2,3,4,6-tetra-*O*-acetylglucopyranoside (411mg, 2.0 eq) and silver carbonate on celite 50% (1.1g, 8 eq) in DCM (5ml) was made up and boiled in darkness. After 3 days, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction of codeine or glucoside starting materials.

45. Synthesis of codeine-6-(2,3,4,6-tetra-*O*-acetylglucopyranoside) 82

i) A solution of codeine (150mg, 0.5mmol), bromo-2,3,4,6-tetra-*O*-acetylglucopyranoside (411mg, 2.0 eq) and silver carbonate on celite 50% (1.1g, 8 eq) in toluene (5ml) was made up and boiled in darkness. After 5 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated complete conversion to 2 new compounds (R_F values: 0.6 and 0.7(main spot) c.f. codeine = 0.45). The mixture was cooled, filtered (washing with chloroform), and the filtrate was concentrated *in vacuo* and flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) to afford a brown oil (100mg, 30%).

δ_H as below.

ii) A solution of codeine (150mg, 0.5mmol), bromo-2,3,4,6-tetra-*O*-acetylglucopyranoside (411mg, 2.0 eq) and silver carbonate on celite 50% (230mg, 1.0

eq) in toluene (5ml) was made up and boiled in darkness. A further portion of silver carbonate on celite (1 eq) was added every 2 hours. After 10 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated complete conversion to 2 new compounds (R_F values: 0.6 and 0.7 (main spot) c.f. codeine = 0.45). The mixture was cooled, filtered (washing with chloroform), and the filtrate was concentrated *in vacuo* to a dark oil. This was taken up in ether and extracted into cold 1% acetic acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) and the product was crystallised in isopropanol to afford colourless needles (88mg, 28%).

m.p. 180-181°C;

R_F 0.7 (mobile phase = 10% methanol/chloroform);

λ_{\max} 3014 (s(brd), arom C-H, C=C), 1754 (s, ester C=O);

δ_H 6.58 (1 H, d, J 8.0, C²-H), 6.47 (1 H, d, J 8.1, C¹-H), 5.64 (1 H, d-m, $J_{7,8}$ 9.5, C⁷-H), 5.28 (1 H, dm, $J_{8,7}$ 10.0, C⁸-H), 5.24 (1 H, t, J 9.5, C³-H), 5.08 (1 H, t, J 9.7, C⁴-H), 5.04 (1 H, t, J 8.5, C²-H), 4.88 (2 H, d+m, $J_{1,2}$ 7.5, C¹-H, C⁵-H), 4.28 (1 H, s(brd), C⁶-H), 4.25 (1 H, dd, J_{gem} 12.0, $J_{6,5}$ 4.4, C⁶-H), 4.11 (1 H, dd, J_{gem} 12.0, $J_{6,5}$ 2.0, C⁶-H), 3.73 (4 H, s+m, OCH₃, C⁵-H), 3.30 (1 H, m, C⁹-H), 3.00 (1 H, d, J_{gem} 18.7, C¹⁰-H _{β}), 2.59 (1 H, s(brd), C¹⁴-H), 2.54 (1 H, dd(brd), J_{gem} 10.0, $J_{16,15}$ 4.0, C¹⁶-H_{eq}), 2.39 (3 H, s, N-CH₃), 2.0-2.4 (2 H, m, C¹⁵-H_{ax}, C¹⁶-H_{ax}), 2.25 (1 H, dd, J_{gem}

19.0, $J_{10,9}$ 6.0, C^{10} -H $_{\alpha}$), 2.11 (3 H, s, OAc), 2.03 (3 H, s, OAc), 1.99 (3 H, s, OAc), 1.97 (3 H, s, OAc), 1.84 (1 H, dm, J_{gem} 13.0, C^{15} -H $_{eq}$);

δ_C 170.5 (OAc), 170.0 (OAc), 169.7 (OAc), 169.3 (OAc), 147.4 (4), 142.0 (3), 130.5 (12), 130.3 (7), 128.8 (8), 127.0 (11), 118.8 (1), 113.3 (2), 98.1 (1), 88.3 (5), 72.8 (5), 72.1 (3), 71.8 (2), 71.2 (4), 68.5 (6), 61.9 (6), 58.7 (9), 56.2 (OCH $_3$), 46.3 (16), 43.5 (13), 43.0 (NCH $_3$), 41.1 (14), 36.0 (15), 20.6 (Ac), 20.5 (2Ac), 20.4 (Ac), 20.3 (10);

m/z (FAB) 630 (M^+ +H);

(Found: C, 60.5; H, 6.25; N, 2.16. C $_{32}$ H $_{39}$ O $_{12}$ N requires C, 61.0; H, 6.25; N, 2.23%).

46. Synthesis of 3-'butyldimethylsilylmorphine-6-(2,3,4,6-tetra-*O*-acetylglucopyranoside) **83**

A solution of 3-'butyldimethylsilylmorphine **57** (600mg, 1.5mmol), bromo-2,3,4,6-tetra-*O*-acetylglucopyranoside (1.23g, 2.0 eq) and silver carbonate on celite 50% (3.3g, 8 eq) in toluene (15ml) was made up and boiled in darkness. After 8 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated complete conversion to 2 new compounds (R_F values: 0.5 and 0.6 (main spot) c.f. **57** = 0.4). The mixture was cooled, filtered (washing with chloroform), and the filtrate was concentrated *in vacuo* to a dark oil. This was taken up in ether and extracted into cold 1% acetic acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic

layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) to afford a brown oil (150mg, 14%).

δ_{H} 6.56 (1 H, d, J 8.1, C²-H), 6.43 (1 H, d, J 8.1, C¹-H), 5.74 (1 H, d-m, $J_{7,8}$ 10.0, C⁷-H), 5.29 (1 H, dt, $J_{8,7}$ 10.0, $J_{8,14}$ 2.5, C⁸-H), 5.23 (1 H, t, J 9.3, C³-H), 5.12 (1 H, t, J 9.5, C⁴-H), 5.02 (1 H, dd, $J_{2,3}$ 9.0, $J_{2,1}$ 8.0, C²-H), 4.90 (1 H, d, $J_{1,2}$ 8.0, C¹-H), 4.84 (1 H, dd, $J_{5,6}$ 6.0, $J_{5,7}$ 1.0, C⁵-H), 4.25 (1 H, dd, J_{gem} 12.0, $J_{6,5}$ 5.0, C⁶-H), 4.23 (1 H, m, C⁶-H), 4.15 (1 H, dd, J_{gem} 12.0, $J_{6,5}$ 2.5, C⁶-H), 3.77 (1 H, ddd, $J_{5,4}$ 9.5, $J_{5,6}$ 5.0, $J_{5,6}$ 2.5, C⁵-H), 3.35 (1 H, dd, $J_{9,10\alpha}$ 5.5, $J_{9,14}$ 2.0, C⁹-H), 3.02 (1 H, d, J_{gem} 18.7, C¹⁰-H $_{\beta}$), 2.6 (2 H, m, C¹⁴-H, C¹⁶-H $_{\text{eq}}$), 2.44 (3 H, s, N-CH₃), 2.0-2.5 (2 H, m, C¹⁵-H $_{\text{ax}}$, C¹⁶-H $_{\text{ax}}$), 2.32 (1 H, dd, J_{gem} 18.7, $J_{10,9}$ 5.5, C¹⁰-H $_{\alpha}$), 2.08 (3 H, s, OAc), 2.06 (3 H, s, OAc), 2.04 (3 H, s, OAc), 2.02 (3 H, s, OAc), 1.84 (1 H, d(brd), J_{gem} 12.0, C¹⁵-H $_{\text{eq}}$), 0.97 (9 H, s, ^tBuSi), 0.18 (3 H, s, CH₃Si), 0.14 (3 H, s, CH₃Si).

47. Synthesis of morphine-6-(2,3,4,6-tetra-*O*-acetylglucopyranoside) **87**

A solution of 3-^tbutyldimethylsilylmorphine-6-(2,3,4,6-tetra-*O*-acetylglucopyranoside) **83** (70mg, 0.1mmol) and TBAF in THF (1.1M, 0.45ml, 5 eq) in THF (1ml) was stirred for 15 hours after which time, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated complete conversion. The solution was concentrated *in vacuo* to a dark oil. This was taken up in ether and extracted into cold 1% acetic

acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) to afford a colourless solid (12mg, 20%).

R_F 0.4 (mobile phase = 10% methanol/chloroform);

δ_{H} 6.65 (1 H, d, J 8.2, C²-H), 6.47 (1 H, d, J 8.2, C¹-H), 5.72 (1 H, d-m, $J_{7,8}$ 9.9, C⁷-H), 5.30 (1 H, dm, $J_{8,7}$ 10.0, C⁸-H), 5.28 (1 H, t, J 9.3, C³-H), 5.10 (1 H, t, J 9.7, C⁴-H), 5.08 (1 H, dd, $J_{2,3}$ 9.5, $J_{2,1}$ 7.5, C²-H), 4.82 (1 H, d, $J_{5,6}$ 6.5, C⁵-H), 4.74 (1 H, d, $J_{1,2}$ 7.6, C¹-H), 4.25 (1 H, dd, J_{gem} 12.5, $J_{6,5}$ 4.5, C⁶-H), 4.20 (1 H, m, C⁶-H), 4.13 (1 H, dd, J_{gem} 12.5, $J_{6,5}$ 2.5, C⁶-H), 3.77 (1 H, m, C⁵-H), 3.39 (1 H, s(brd), OH), 3.27 (1 H, m, C⁹-H), 3.00 (1 H, d, J_{gem} 18.7, C¹⁰-H _{β}), 2.70 (1 H, s(brd), C¹⁴-H), 2.67 (1 H, dm, J_{gem} 12.0, C¹⁶-H_{eq}), 2.47 (3 H, s, N-CH₃), 2.0-2.5 (2 H, m, C¹⁵-H_{ax}, C¹⁶-H_{ax}), 2.35 (1 H, dd, J_{gem} 18.7, $J_{10,9}$ 6.0, C¹⁰-H _{α}), 2.18 (3 H, s, OAc), 2.07 (3 H, s, OAc), 2.04 (6 H, s, 2xOAc), 1.90 (1 H, d(brd), J_{gem} 12.0, C¹⁵-H_{eq}).

48. Synthesis of 3-acetylmorphine-6-(2,3,4,6-tetra-*O*-acetylglucopyranoside) **88**

A solution of 3-acetylmorphine **47** (200mg, 0.61mmol), bromo-2,3,4,6-tetra-*O*-acetylglucopyranoside (500mg, 2.0 eq) and silver carbonate on celite 50% (250mg, 1 eq) in toluene (5ml) was made up and boiled in darkness. A further portion of silver carbonate on celite (1 eq) was added every 2 hours. After 10 hours, t.l.c. analysis

(mobile phase = 10% methanol/chloroform) indicated complete conversion to 2 new compounds (R_F values: 0.55 and 0.65(main spot) c.f. **47** = 0.45). The mixture was cooled, filtered (washing with chloroform), and the filtrate was concentrated *in vacuo* to a brown oil. This was taken up in ether and extracted into cold 1% acetic acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) to afford a brown oil (110mg, 27%).

R_F 0.65 (mobile phase = 10% methanol/chloroform);

λ_{\max} 3022 (s(brd), arom C-H, C=C), 1752 (s, ester C=O);

δ_H 6.73 (1 H, d, J 8.0, C²-H), 6.56 (1 H, d, J 8.2, C¹-H), 5.71 (1 H, d-m, $J_{7,8}$ 9.9, C⁷-H), 5.30 (1 H, dt, $J_{8,7}$ 10.0, $J_{8,14;8,6}$ 3.0, C⁸-H), 5.25 (1 H, t, J 9.0, C³-H), 5.11 (1 H, t, J 9.5, C⁴-H), 5.10 (1 H, dd, $J_{2,3}$ 9.7, $J_{2,1}$ 7.5, C²-H), 4.90 (1 H, d, $J_{5,6}$ 6.0, C⁵-H), 4.81 (1 H, d, $J_{1,2}$ 7.5, C¹-H), 4.25 (2 H, dd+s(brd), J_{gem} 9.5, $J_{6,5}$ 4.5, C⁶-H, C⁶-H), 4.15 (1 H, dd, J_{gem} 9.5, $J_{6,5}$ 2.2, C⁶-H), 3.78 (1 H, ddd, $J_{5,4}$ 9.5, $J_{5,6}$ 4.5, $J_{5,6}$ 2.2, C⁵-H), 3.40 (1 H, m, C⁹-H), 3.06 (1 H, d, J_{gem} 19.2, C¹⁰-H $_{\beta}$), 2.69 (2 H, m, C¹⁴-H, C¹⁶-H $_{\text{eq}}$), 2.46 (3 H, s, N-CH₃), 2.0-2.4 (3 H, m, C¹⁵-H $_{\text{ax}}$, C¹⁶-H $_{\text{ax}}$, C¹⁰-H $_{\alpha}$), 2.32 (3 H, s, ArOAc), 2.11 (3 H, s, OAc), 2.07 (3 H, s, OAc), 2.04 (3 H, s, OAc), 2.02 (3 H, s, OAc), 1.93 (1 H, dm, J_{gem} 12.0, C¹⁵-H $_{\text{eq}}$);

δ_C 132.0 (3), 130.5 (12), 132.6 (7), 128.6 (8), 119.2 (1), 121.9 (2), 99.8 (**1**), 89.8 (5), 73.9 (**5**), 72.7 (**3**), 71.9 (**2**), 71.2 (**4**), 68.3 (6), 61.9 (**6**), 58.7 (9), 46.2 (16), 43.0

(NCH₃), 40.9 (14), 34.1 (15), 20.7 (2Ac), 20.6 (2Ac), 20.6 (Ac), not visible (5xOAc, 4, 11, 13, 10);

m/z (FAB) 658 (M⁺+H);

(Found: C, 58.8; H, 6.21; N, 1.88. C₃₃H₃₉O₁₃N.H₂O requires C, 58.3; H, 6.13; N, 2.06%).

49. Synthesis of codeine-6-glucoside 84

Codeine-2,3,4,6-tetra-*O*-acetylglucopyranoside **82** (80mg, 0.13mmol) was dissolved in a solution of sodium hydroxide (25mg, 5 eq) in water (5ml) and stood for 1 hour. T.l.c. analysis (mobile phase = 80% methanol/chloroform) indicated complete conversion to a new compound, R_F = 0.25. Acetic acid (0.5ml) was added and the solution was concentrated *in vacuo*, dissolved in 1% acetonitrile/water and passed through a Waters Sep-pak C-18 cartridge, flushing with the same mobile phase to afford a colourless solid (40mg, 68%).

m.p. 240-260°C (dec.);

R_F 0.3 (mobile phase = 80% methanol/chloroform);

δ_H (D₂O) 6.85 (1 H, d, *J* 8.1, C²-H), 6.71 (1 H, d, *J* 8.1, C¹-H), 5.77 (1 H, d, *J*_{7,8} 9.7, C⁷-H), 5.37 (1 H, d, *J*_{8,7} 9.7, C⁸-H), 5.21 (1 H, d, *J*_{5,6} 5.8, C⁵-H), 4.67 (1 H, d, *J*_{1,2} 7.7, C¹-H), 4.53 (1 H, s(brd), C⁶-H), 4.02 (1 H, s(brd), C⁹-H), 3.79 (3 H, s, OCH₃), 3.4 (1

H, m, C⁵-H), 3.50 (1 H, t, *J* 9.0, C³-H), 3.32 (1 H, t, *J* 9.0, C⁴-H), 3.40 (1 H, t, *J* 8.5, C²-H), 3.21 (1 H, d, *J*_{gem} 19, C¹⁰-H_β), 3.2 (1 H, m, C¹⁴-H), 2.9 (1 H, t(brd), *J* 14, C¹⁶-H_{ax}), 2.83 (3 H, s, N-CH₃), 2.8-2.9 (2 H, m, C¹⁶-H_{eq}, C¹⁰-H_α), 2.26 (1 H, t(brd), *J* 13, C¹⁵-H_{ax}), 2.12 (1 H, d(brd), *J*_{gem} 13, C¹⁵-H_{eq});

δ_C 148.4 (4), 143.9 (3), 133.2 (7), 131.3 (12), 128.9 (8), 127.0 (11), 122.4 (1), 116.3 (2), 103.8 (1), 90.9 (5), 78.1 (5), 77.6 (3), 75.3 (2), 75.1 (4), 71.6 (6), 62.0 (9), 58.5 (OCH₃), 48.6 (16), 44.0 (13), 42.9 (NCH₃), not visible (10), (14), (15).

50. Synthesis of morphine-6-glucoside 86

A solution of morphine-6-(2,3,4,6-tetra-*O*-acetylglucopyranoside) **87** (12mg, 0.02mmol) in sodium methoxide in methanol (0.4ml, 0.2 eq) was stirred and monitored by t.l.c. (mobile phase = 30% methanol/chloroform). Complete reaction was observed after 2 hours and the solution was concentrated *in vacuo*, dissolved in ether and extracted several times into water. Concentration *in vacuo* yielded a colourless solid (9mg, 95%).

m.p. 250-280°C (dec.);

R_F 0.3 (mobile phase = 80% methanol/chloroform);

δ_H (D₂O) 6.57 (2 H, 2d, *J* 8.0, C²-H, C¹-H), 5.75 (1 H, d, *J*_{7,8} 9.5, C⁷-H), 5.40 (1 H, d, *J*_{8,7} 9.5, C⁸-H), 5.10 (1 H, d, *J*_{5,6} 6.0, C⁵-H), 4.68 (1 H, d, *J*_{1,2} 7.9, C¹-H), 4.50 (1 H, s(brd), C⁶-H), 3.83 (1 H, d, *J*_{gem} 12.0, C⁶-H), 3.65 (1 H, d, *J*_{gem} 12.0, C⁶-H), 3.3-3.7 (5

H, m, C⁹-H, C²-H, C³-H, C⁴-H, C⁵-H), 3.08 (1 H, d, J_{gem} 19.0, C¹⁰-H_β), 3.15 (1 H, m, C¹⁴-H), 2.70 (1 H, m, C¹⁶-H_{ax}), 2.48 (3 H, s, N-CH₃), 2.5-2.6 (2 H, m, C¹⁶-H_{eq}, C¹⁰-H_α), 2.10 (1 H, t(brd), J 13.0, C¹⁵-H_{ax}), 1.85 (1 H, d(brd), J_{gem} 13.0, C¹⁵-H_{eq}).

δ_C (D₂O) 149.3 (4), 141.9 (3), 134.7 (7), 133.0 (12), 130.3 (8), 127.4 (11), 123.9 (1), 121.3 (2), 105.2 (1), 91.9 (5), 79.7 (5), 79.3 (3), 76.8 (2), 76.6 (4), 73.1 (6), 64.3 (6), 63.6 (9), 50.2 (16), 45.6 (13), 44.4 (NCH₃), 41.4 (14), 35.7 (15), 26.8 (10).

m/z (FAB) 448 (M⁺+H), 470 (M⁺+Na).

51. Synthesis of codeine-6-methyl (tri-*O*-acetylglucopyranosyl) uronate **50**

A solution of codeine (150mg, 0.5mmol), methyl (bromo-2,3,4-tri-*O*-acetylglucopyranosyl) uronate **48** (411mg, 2.0 eq) and silver carbonate on celite 50% (230mg, 1.0 eq) in toluene (5ml) was made up and boiled in darkness. A further portion of silver carbonate on celite (1 eq) was added every 2 hours. After 10 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated complete conversion to 2 new compounds (R_F values: 0.6 and 0.7(main spot) c.f. codeine = 0.45). The mixture was cooled, filtered (washing with chloroform), and the filtrate was concentrated *in vacuo* to a dark oil. This was taken up in ether and extracted into ice-cold 0.5M hydrochloric acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase =

1.5-3% gradient methanol/chloroform) to afford an oil which was triturated with ether/petroleum ether (30mg, 10%).

m.p. 177-179°C;

R_F 0.7 (mobile phase = 10% methanol/chloroform);

λ_{max} 3019 (s(brd), arom C-H, C=C), 1756 (s, ester C=O);

δ_H 6.63 (1 H, d, *J* 8.2, C²-H), 6.52 (1 H, d, *J* 8.2, C¹-H), 5.68 (1 H, ddt, *J*_{7,8} 9.9, *J*_{7,6} 3.0, *J*_{7,5} 1.6, C⁷-H), 5.34 (1 H, t, *J* 9.2, C³-H), 5.30 (1 H, dt, *J*_{8,7} 10.0, *J*_{8,14;8,6} 3.0, C⁸-H), 5.25 (1 H, t, *J* 9.5, C⁴-H), 5.10 (1 H, dd, *J*_{2,3} 9.0, *J*_{2,1} 7.5, C²-H), 4.98 (1 H, d, *J*_{1,2} 7.5, C¹-H), 4.94 (1 H, dd, *J*_{5,6} 6.0, *J*_{5,7} 1.3, C⁵-H), 4.38 (1 H, dtd, *J*_{6,5} 6.0, *J*_{6,7;6,8} 3.0, *J*_{6,14} 2.0, C⁶-H), 4.12 (1 H, d, *J* 9.5, C⁵-H), 3.76, 3.78 (6 H, 2s, OCH₃+CO₂CH₃), 3.35 (1 H, m, C⁹-H), 3.04 (1 H, d, *J*_{gem} 18.9, C¹⁰-H_β), 2.66 (1 H, m, C¹⁴-H), 2.60 (1 H, dd, *J*_{gem} 12.0, *J*_{16,15} 4.0, C¹⁶-H_{eq}), 2.44 (3 H, s, N-CH₃), 2.40 (1 H, td, *J*_{gem;16,15ax} 12.0, *J*_{16,15eq} 3.5, C¹⁶-H_{ax}), 2.31 (1 H, dd, *J*_{gem} 19.0, *J*_{10,9} 6.5, C¹⁰-H_α), 2.16 (3 H, s, OAc), 2.04 (3 H, s, OAc), 2.03 (3 H, s, OAc), 2.0-2.1 (1 H, m, C¹⁵-H_{ax}), 1.88 (1 H, dm, *J*_{gem} 12.0, C¹⁵-H_{eq}):

δ_C 170.0 (OAc), 169.7 (OAc), 169.4 (OAc), 167.4 (CO₂CH₃), 147.3 (4), 142.1 (3), 130.6 (12), 130.2 (7), 128.8 (8), 127.0 (11), 118.9 (1), 113.2 (2), 97.9 (1), 88.0 (5), 72.7 (5), 72.1 (3), 71.8 (2), 71.2 (4), 69.5 (6), 58.8 (9), 56.2 (OCH₃), 52.8 (CO₂CH₃), 46.4 (16), 43.4 (13), 43.0 (NCH₃), 41.0 (14), 35.9 (15), 20.4 (10);

m/z (FAB) 616 (M⁺+H);

(Found: C, 58.8; H, 5.81; N, 2.30. C₃₁H₃₇O₁₂N requires C, 60.5; H, 6.06; N, 2.28%).

52. Synthesis of 3-acetylmorphine-6-methyl (tri-*O*-acetylglucopyranosyl) uronate

49

A solution of 3-acetylmorphine **47** (240mg, 0.74mmol), methyl (bromo-2,3,4-tri-*O*-acetylglucopyranosyl) uronate **48** (600mg, 2.0 eq) and silver carbonate on celite 50% (600mg, 1.5 eq) in toluene (10ml) was made up and boiled in darkness. A further portion of silver carbonate on celite (1.5 eq) was added every 3 hours. After 6 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated almost complete conversion to 2 new compounds (*R_F* values: 0.55 and 0.65(main spot) c.f. **47** = 0.45). The mixture was cooled, filtered (washing with chloroform), and the filtrate was concentrated *in vacuo* to a dark oil. This was taken up in ether and extracted into ice-cold 0.5M hydrochloric acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) to afford a light oil (210mg, 45%).

m.p. 168-169°C;

R_F 0.65 (mobile phase = 10% methanol/chloroform);

λ_{max} 3014 (s(brd), arom C-H, C=C), 1757 (s, ester C=O);

δ_{H} 6.73 (1 H, d, J 8.1, C²-H), 6.55 (1 H, d, J 8.2, C¹-H), 5.69 (1 H, d-m, $J_{7,8}$ 9.9, C⁷-H), 5.31 (1 H, dt, $J_{8,7}$ 10.0, $J_{8,14;8,6}$ 3.0, C⁸-H), 5.30 (1 H, t, J 7.0, C³-H), 5.26 (1 H, t, J 7.0, C⁴-H), 5.10 (1 H, td, $J_{2,3;2,1}$ 7.0, J 2.5, C²-H), 4.91 (1 H, dd, $J_{5,6}$ 6.6, $J_{5,7}$ 1.0, C⁵-H), 4.90 (1 H, d, $J_{1,2}$ 7.5, C¹-H), 4.31 (1 H, dtd, $J_{6,5}$ 6.0, $J_{6,7;6,8}$ 3.0, $J_{6,14}$ 2.0, C⁶-H), 4.12 (1 H, d, J 7.0, C⁵-H), 3.74 (3 H, s, CO₂CH₃), 3.37 (1 H, dd, $J_{9,10\alpha}$ 6.0, $J_{9,14}$ 3.1, C⁹-H), 3.05 (1 H, d, $J_{\beta:\alpha}$ 18.9, C¹⁰-H _{β}), 2.65 (1 H, m, C¹⁴-H), 2.60 (1 H, dd, J_{gem} 12.0, $J_{16,15}$ 4.5, C¹⁶-H_{eq}), 2.43 (3 H, s, N-CH₃), 2.0-2.4 (3 H, m, C¹⁵-H_{ax}, C¹⁶-H_{ax}, C¹⁰-H _{α}), 2.31 (3 H, s, ArOAc), 2.11 (3 H, s, OAc), 2.04 (6 H, s, 2xOAc), 1.92 (1 H, dm, J_{gem} 11.0, C¹⁵-H_{eq});

δ_{C} 170.1 (OAc), 169.3 (OAc), 169.2 (OAc), 168.7 (OAc), 167.4 (CO₂CH₃), 150.1 (4), 132.3 (3), 131.6 (11), 131.4 (12), 130.2 (7), 128.8 (8), 121.8 (2), 119.1 (1), 99.1 (1), 89.4 (5), 73.3 (5), 72.6 (3), 71.9 (2), 71.1 (4), 69.2 (6), 58.6 (9), 52.8 (CO₂CH₃), 46.2 (16), 43.5 (13), 43.5 (NCH₃), 41.0 (14), 35.6 (15), 20.6 (2Ac), 20.5 (2Ac), 20.8 (10);

m/z (FAB) 644 (M⁺+H);

(Found: C, 59.3; H, 5.81; N, 2.17. C₃₂H₃₇O₁₃N requires C, 59.7; H, 5.79; N, 2.18%).

53. Synthesis of codeine-6-methyl (tri-*O*-acetylglucopyranosyl) uronate 50

A solution of codeine (100mg, 0.33mmol), methyl (bromo-2,3,4-tri-*O*-acetylglucopyranosyl) uronate **48** (280mg, 2.0 eq), silver carbonate (170mg, 2.0 eq)

and celite (500g) in toluene (5ml) was made up and boiled in darkness. A further portion of silver carbonate (2 eq) was added every 3 hours. After 6 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated complete conversion to 2 new compounds (R_F values: 0.6 and 0.7(main spot) c.f. codeine = 0.45). The mixture was cooled, filtered (washing with chloroform), and the filtrate was concentrated *in vacuo* to a dark oil. This was taken up in ether and extracted into ice-cold 0.5M hydrochloric acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) to afford an oil which was triturated with ether/ethyl acetate (15mg, 7%).

δ_H as previous.

54. Attempted synthesis of codeine-6-methyl (tri-*O*-acetylglucopyranosyl) uronate

50

A solution of codeine (100mg, 0.33mmol), methyl (bromo-2,3,4-tri-*O*-acetylglucopyranosyl) uronate **48** (280mg, 2.0 eq) and celite (500g) in toluene (5ml) was made up and boiled in darkness. After 6 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated slight conversion to a new compound (R_F = 0.6 c.f. codeine = 0.45). The mixture was cooled, filtered (washing with chloroform), and the filtrate was concentrated *in vacuo* to a dark oil. This was taken up in ether and

extracted into ice-cold 0.5M hydrochloric acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) to afford an oil which was triturated with ether/petroleum ether (3mg). Data suggests formation of codeine-6-acetate.

δ_{H} 6.67 (1 H, d, J 8.1, C²-H), 6.55 (1 H, d, J 8.3, C¹-H), 5.65 (1 H, d-m, $J_{7,8}$ 9.9, C⁷-H), 5.44 (1 H, dt, $J_{8,7}$ 9.9, $J_{8,14;8,6}$ 2.5, C⁸-H), 5.09 (1 H, dd, $J_{5,6}$ 6.6, $J_{5,7}$ 1.1, C⁵-H), 4.21 (1 H, s(brd), C⁶-H), 3.45 (1 H, s(brd), C⁹-H), 3.86 (3 H, s, OMe), 3.05 (1 H, d, $J_{\beta,\alpha}$ 19.0, C¹⁰-H $_{\beta}$), 2.49 (3 H, s, N-CH₃), 2.0-2.85 (5 H, m, C¹⁰-H $_{\alpha}$, C¹⁴-H, C¹⁶-H $_{\text{eq}}$, C¹⁵-H $_{\text{ax}}$, C¹⁶-H $_{\text{ax}}$), 2.17 (3 H, s, OAc), 1.90 (1 H, dd, J_{gem} 13.0, $J_{15,16}$ 3.0, C¹⁵-H $_{\text{eq}}$);

m/z (FAB) 342 ($M^+ + H$).

55. Synthesis of morphine-6-methyl glucopyranosyl uronate 90

3-Acetylmorphine-6-methyl (tri-*O*-acetylglucopyranosyl) uronate **49** (160mg, 0.24mmol) was dissolved in a solution of sodium in methanol, 0.22mg/ml (5ml, 0.2 eq) and boiled, monitoring by t.l.c. analysis (mobile phase = 25% methanol/chloroform). After 3 hours, the reaction was complete. The mixture was concentrated *in vacuo* to an oil, to which was added water (10ml) and the impurities were extracted into ethyl acetate. The aqueous layer was collected and concentrated *in vacuo* to an off-white

solid (80mg, 68%). Data indicated presence of **40** so crude material was carried through to next step.

56. Synthesis of morphine-6-glucuronide **40**

i) A solution of morphine-6-methyl glucopyranosyl uronate **90** (55mg, 0.115mmol) in 0.43N barium hydroxide (0.2ml, 0.75 eq) was stood for 1 hour before 2N oxalic acid was added to pH 6. The resulting suspension was filtered, and the filtrate was concentrated *in vacuo* to afford an off-white crystalline solid (48mg, 90%). This was shown to contain inorganic contaminants.

m.p. 230-280°C (dec.);

R_F 0.3 (mobile phase = 80% methanol/chloroform);

δ_{H} (D₂O) 6.73 (1 H, d, J 8.0, C²-H), 6.65 (1 H, d, J 8.0, C¹-H), 5.82 (1 H, d, $J_{7,8}$ 9.9, C⁷-H), 5.37 (1 H, d, $J_{8,7}$ 9.9, C⁸-H), 5.22 (1 H, dd, $J_{5,6}$ 5.7, C⁵-H), 4.71 (1 H, d, $J_{1,2}$ 7.7, C¹-H), 4.56 (1 H, m, C⁶-H), 4.15 (1 H, m, C⁹-H), 3.71 (1 H, d, J 9.0, C⁵-H), 3.53 (1 H, t, J 9.0, C³-H), 3.48 (1 H, t, $J_{2,3;2,1}$ 8.0, C²-H), 3.37 (1 H, t, J 9.0, C⁴-H), 3.22 (1 H, d(brd), $J_{\beta:\alpha}$ 21, C¹⁰-H _{β}), 2.95 (3 H, s, N-CH₃), 2.8-3.4 (4 H, m, , C¹⁴-H, C¹⁶-H_{eq}, C¹⁶-H_{ax}, C¹⁰-H _{α}), 2.32 (1 H, tm, J 9, C¹⁵-H_{ax}), 2.13 (1 H, dm, J_{gem} 13.0, C¹⁵-H_{eq});

m/z (FAB) 462 (M⁺+H).

ii) A stirred suspension of morphine-6-methyl glucopyranosyl uronate **90** (10mg, 0.02mmol) and Dowex 50(H) ion-exchange resin (2mg) in water (1ml) was boiled for 8 hours. T.l.c. analysis (mobile phase = 80% methanol/chloroform) indicated conversion to material with lower R_F value. The solution was cooled, filtered, and concentrated *in vacuo* to an off-white solid (6mg, 60%).

R_F 0.3 (mobile phase = 80% methanol/chloroform);

δ_H (D_2O) 6.73 (1 H, d, J 8.0, C^2 -H), 6.65 (1 H, d, J 8.0, C^1 -H), 5.82 (1 H, d, $J_{7,8}$ 9.9, C^7 -H), 5.37 (1 H, d, $J_{8,7}$ 9.9, C^8 -H), 5.22 (1 H, dd, $J_{5,6}$ 5.7, C^5 -H), 4.71 (1 H, d, $J_{1,2}$ 7.7, C^1 -H), 4.56 (1 H, m, C^6 -H), 4.15 (1 H, m, C^9 -H), 3.71 (1 H, d, J 9.0, C^5 -H), 3.53 (1 H, t, J 9.0, C^3 -H), 3.48 (1 H, t, $J_{2,3;2,1}$ 8.0, C^2 -H), 3.37 (1 H, t, J 9.0, C^4 -H), 3.22 (1 H, d(brd), $J_{\beta,\alpha}$ 21, C^{10} -H $_{\beta}$), 2.95 (3 H, s, N-CH $_3$), 2.8-3.4 (4 H, m, , C^{14} -H, C^{16} -H $_{eq}$, C^{16} -H $_{ax}$, C^{10} -H $_{\alpha}$), 2.32 (1 H, tm, J 9, C^{15} -H $_{ax}$), 2.13 (1 H, dm, J_{gem} 13.0, C^{15} -H $_{eq}$);

δ_C 180.9 (CO $_2$ H), 154.1 (4), 146.4 (3), 139.6 (7), 137.5 (12), 134.8 (8), 131.8 (11), 128.9 (1), 126.3 (2), 110.2 (1), 96.6 (5), 83.6 (5), 83.2 (3), 81.5 (2), 81.3 (4), 79.6 (6), 69.1 (9), 55.7 (16), 49.7 (NCH $_3$), 29.4 (10), 50.0 (13), 47.0 (14), 40.9 (15).

m/z (FAB) 462 (M^+ +H);

(Found: C, 51.4; H, 6.02; N, 2.45. C $_{23}$ H $_{27}$ O $_9$ N.1.1H $_2$ O requires C, 51.0; H, 5.93; N, 2.37%).

iii) A stirred suspension of 3-acetylmorphine-6-methyl (tri-*O*-acetylglucopyranosyl) uronate **49** (170mg, 0.26mmol) and Dowex 50(H) ion-exchange resin (30mg) in water (10ml) was boiled for 5 hours. T.l.c. analysis (mobile phase = 80% methanol/chloroform) indicated very slight conversion to material with lower R_F value. The reaction was continued for a further 20 hours when t.l.c. analysis indicated complete conversion. The solution was cooled, filtered, and concentrated *in vacuo* to an off-white solid (113mg). N.m.r. extremely complex with several acetate peaks present, no methyl ester peak, and an NMe shift at 2.95 p.p.m.

δ_H (D_2O) 6.65 (2 H, m, C¹-H, C²-H), 2.95 (3 H, s, N-CH₃), 2.16, 2.11, 2.05, 2.04, 2.01 (~7 H, 5s, OAc);

m/z (FAB) 630 ($M^+ + H$), 588 (-Ac), 546 (-Ac), 504 (-Ac), 462 (-Ac).

iv) A stirred suspension of 3-acetylmorphine-6-methyl (tri-*O*-acetylglucopyranosyl) uronate **49** (125mg, 0.2mmol) and Amberlite IRA-410 ion-exchange resin (5mg) in water (10ml) was boiled for 3 days. T.l.c. analysis (mobile phase = 80% methanol/chloroform) indicated complete conversion. The solution was cooled, filtered, and concentrated *in vacuo* to an off-white solid (59mg) which was shown by n.m.r. to contain an acetate group. The product was taken up with methanol (5ml) and 2N ammonia (1ml) was added. After standing for 1 day, evaporation *in vacuo* gave an off-white solid (49mg, 55%).

δ_H as i).

57. Synthesis of codeine-6-glucuronide 41

A stirred suspension of codeine-6-methyl (tri-*O*-acetylglucopyranosyl) uronate **50** (20mg, 0.033mmol) and Amberlite IRA-410 ion-exchange resin (5mg) in water (5ml) was boiled for 12 hours. T.l.c. analysis (mobile phase = 80% methanol/chloroform) indicated complete conversion to a new compound, $R_F = 0.3$. The solution was cooled, filtered, and concentrated ammonium hydroxide (2ml) in water (3ml) and methanol (5ml) was added. The mixture was left to stand for 2 days before t.l.c. analysis indicated complete conversion to another new compound, $R_F = 0.25$. The solution was washed with chloroform and concentrated *in vacuo* to an oil which was dissolved in 1% acetonitrile/water and passed through a Waters Sep-pak C-18 cartridge, flushing with the same mobile phase to afford a colourless solid which was shown still to contain ammonium acetate. This impurity was removed by freeze-drying (5mg, 35%).

m.p. 240-260°C (dec.);

R_F 0.3 (mobile phase = 80% methanol/chloroform);

δ_H (D₂O) 6.90 (1 H, d, J 8.4, C²-H), 6.75 (1 H, d, J 8.4, C¹-H), 5.82 (1 H, d, $J_{7,8}$ 9.7, C⁷-H), 5.37 (1 H, d, $J_{8,7}$ 9.9, C⁸-H), 5.25 (1 H, d, $J_{5,6}$ 5.7, C⁵-H), 4.68 (1 H, d, $J_{1,2}$ 7.9, C¹-H), 4.38 (1 H, m, C⁶-H), 4.18 (1 H, m, C⁹-H), 3.81 (3 H, s, OCH₃), 3.71 (1 H, d, J 9.3, C⁵-H), 3.54 (1 H, t, J 9.0, C³-H), 3.50 (1 H, t, J 9.5, C⁴-H), 3.36 (1 H, t, J 8.5, C²-H), 3.26 (1 H, d(brd), J_{gem} 20, C¹⁰-H β), 2.97 (3 H, s, N-CH₃), 2.85-3.15 (4 H, m,

C^{14} -H, C^{16} -H_{eq}, C^{16} -H_{ax}, C^{10} -H_α), 2.33 (1 H, t(brd), J 12, C^{15} -H_{ax}), 2.12 (1 H, d(brd), J_{gem} 9, C^{15} -H_{eq});

δ_c 176.5 (CO₂H), 147.2 (4), 142.9 (3), 125.0 (11), 129.7 (12), 132.4 (7), 126.8 (8), 115.2 (2), 121.3 (1), 102.3 (1), 89.3 (5), 77.1 (5), 76.2 (3), 73.9 (2), 73.5 (4), 72.6 (6), 61.3 (9), 57.2 (OCH₃), 42.6 (16), 41.5 (NCH₃), 19.0 (10), not visible (13), (14), (15);

m/z (FAB) 476 ($M^+ + H$).

58. Synthesis of methyl (1,2,3,4-tetra-*O*-isobutanoylglucopyranosyl) uronate 92

A solution of methyl glucopyranosyl uronate **55** (11.8g, 55mmol) in pyridine (34ml) and DCM (35ml) was cooled to 0°C and isobutanoyl chloride (53.2g, 52.3ml, 4.8 eq) was added dropwise over 2 hours. The solution was stirred at 20°C for 2 days and t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) showed complete conversion to a new compound, R_F = 0.9. The solution was diluted with DCM (150ml), washed with dilute hydrochloric acid (100ml) and subsequently with saturated sodium hydrogen carbonate, dried over sodium sulfate, filtered, and concentrated *in vacuo* to a black oil which was crystallised from petroleum ether to afford colourless prisms (8.13g). A 2nd batch was obtained after concentrating the mother liquor giving an off-white solid which was recrystallised from petroleum ether to afford more colourless prisms (3.72g, =11.8g total, 43%).

R_F 0.9 (mobile phase = 40% ethyl acetate/petroleum ether);

δ_H 5.81 (1 H, d, J 7.7, C¹-H), 5.35 (1 H, t, J 9.0, C³-H), 5.29 (1 H, t, J 9.0, C⁴-H), 5.18 (1 H, t, J 7.9, C²-H), 4.25 (1 H, d, J 9.3, C⁵-H), 3.78 (3 H, s, ester CH₃), 2.55 (4 H, m, 4x OC(O)CH(CH₃)₂), 1.10 (24 H, m, 8x ^{*i*}butanoyl-CH₃).

59. Attempted synthesis of methyl (2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate

93

Dry ammonia gas was bubbled through DCM (200ml) at -4°C over 1 hour before methyl (1,2,3,4-tetra-*O*-isobutanoylglucopyranosyl) uronate **92** (8.0g, 16mmol) was added and the solution was stirred at 0°C for 3.5 hours. T.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated no reaction. The solution was concentrated *in vacuo* giving complete recovery of the starting material as a colourless solid (8.0g).

60. Synthesis of methyl (2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **93**

A solution of methyl (1,2,3,4-tetra-*O*-isobutanoylglucopyranosyl) uronate **92** (8.0g, 16mmol) in DCM (200ml) was made up and dry ammonia gas was bubbled through at 0°C for 12 hours. T.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether)

indicated partial conversion to a new compound, $R_F = 0.55$. Bubbling of ammonia gas was continued at 20°C for a further 10 hours during which time the solution had concentrated to around 80ml. T.l.c. analysis now showed almost complete conversion. Nitrogen gas was bubbled through the mixture for 20 minutes and the solution was washed with ice-cold 10% hydrochloric acid and subsequently with water, dried over sodium sulfate, filtered, and concentrated *in vacuo* to an oil which was flash chromatographed to afford a colourless crystalline solid (4.1g, 60%).

R_F 0.55 (mobile phase = 40% ethyl acetate/petroleum ether);

δ_H 5.57 (1 H, t, J 9.5, C³-H), 5.50 (1 H, d, J 7.8, C¹-H), 5.24 (1 H, t, J 9.5, C⁴-H), 5.11 (1 H, dd, $J_{2,3}$ 9.0, $J_{2,1}$ 8.0, C²-H), 4.25 (1 H, d, J 9.5, C⁵-H), 3.76 (3 H, s, ester CH₃), 3.15 (1 H, s(brd), OH), 2.55 (3 H, m, 3x OC(O)CH(CH₃)₂), 1.15 (18 H, m, 6x *i*-butanoyl-CH₃).

61. Attempted synthesis of methyl (trichloroacetimidyl-2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **91**

A solution of methyl (2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **93** (3.9g, 9.3mmol) in DCM (40ml) was made up and trichloroacetonitrile (5.8g, 4.0ml, 40mmol) was added. The solution was stirred for 10 minutes before potassium carbonate (1.3g, 2 charge eq) was added and the reaction was monitored by t.l.c. (mobile phase = 40% ethyl acetate/petroleum ether). After 2 hours, partial conversion was shown and ~70% conversion was indicated after 24 hours. After 2 days, t.l.c.

analysis indicated lower conversion, suggesting an equilibrium which was shifting back, possibly due to the volatility of trichloroacetonitrile. A further portion (4ml) was added and after 2 hours, t.l.c. analysis indicated over 90% conversion. The solution was filtered, washed with water, dried over sodium sulfate, and concentrated to an oil which was crystallised and recrystallised from isopropanol to colourless prisms (1.3g, 25%). This was shown to be the coupling product of **91** and isopropanol as the β anomer.

R_F 0.85 (mobile phase = 40% ethyl acetate/petroleum ether);

δ_H 5.33 (1 H, t, J 9.3, C³-H), 5.22 (1 H, t, J 9.7, C⁴-H), 5.01 (1 H, dd, $J_{2,3}$ 9.3, $J_{2,1}$ 8.0, C²-H), 4.65 (1 H, d, J 7.7, C¹-H), 4.07 (1 H, d, J 9.7, C⁵-H), 3.96 (1 H, sept, J 6.0, ^{*i*}propyl CH), 3.74 (3 H, s, ester CH₃), 2.50 (3 H, m, 3x OC(O)CH(CH₃)₂), 1.05-1.25 (24 H, m, 6x ^{*i*}butanoyl-CH₃ + ^{*i*}propyl CH₃).

m/z (FAB) 461 ($M^+ + H$) 418 ($M^+ + H - OH$) 401 ($M^+ - \text{butanoyl}$).

62. Synthesis of methyl (trichloroacetimidyl-2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **91**

A solution of methyl (2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **93** (1.3g, 3.1mmol) in DCM (20ml) was made up and trichloroacetonitrile (4.35g, 3.0ml, 30mmol) was added. The solution was stirred for 10 minutes before potassium carbonate (500mg, 2.2 charge eq) was added and the reaction was monitored by t.l.c.

(mobile phase = 40% ethyl acetate/petroleum ether). After 24 hours, t.l.c. analysis indicated over 90% conversion. The solution was filtered, washed with water, dried over sodium sulfate, and concentrated to an oil which was flash chromatographed (mobile phase = 12% ethyl acetate/petroleum ether) to afford a colourless solid (1.36g, 75%). Product shown to be the α anomer.

R_F 0.85 (mobile phase = 40% ethyl acetate/petroleum ether);

δ_H 8.75 (1 H, s(brd)), 6.55 (1 H, d, J 3.5, C¹-H), 5.58 (1 H, t, J 9.5, C³-H), 5.22 (1 H, t, J 9.5, C⁴-H), 5.10 (1 H, dd, $J_{2,3}$ 9.0, $J_{2,1}$ 3.5, C²-H), 4.36 (1 H, d, J 9.5, C⁵-H), 3.78 (3 H, s, ester CH₃), 2.60 (3 H, m, 3x OC(O)CH(CH₃)₂), 1.10 (18 H, m, 6x ⁱbutanoyl-CH₃).

63. Synthesis of 3-acetylmorphine-6-methyl (tri-*O*-isobutanoylglucopyranosyl)uronate **95**

A solution of 3-acetylmorphine **47** (0.186g, 0.57mmol) and methyl (trichloroacetimidyl-2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **91** (640mg, 2.0 eq) in DCM (2ml) was made up and boron trifluoride etherate (162mg, 0.14ml, 2.0 eq) was added dropwise. The mixture was stirred, monitoring by t.l.c. analysis (mobile phase = 10% methanol/chloroform). After 16 hours, several compounds were present, including both starting materials and a new compound giving a strong spot, R_F = 0.7. The mixture was quenched with saturated sodium hydrogen carbonate, extracted into

DCM and concentrated *in vacuo* to an oil which was taken up in ether and extracted into ice-cold 0.5M hydrochloric acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase = 1.5-3% gradient methanol/chloroform) to afford an oil which was triturated with ether/petroleum ether (60mg, 15%).

m.p. 186°C (lit. 188-189°C);

R_F 0.80 (mobile phase = 10% methanol/chloroform);

δ_{H} 6.72 (1 H, d, J 8.1, C²-H), 6.54 (1 H, d, J 8.1, C¹-H), 5.68 (1 H, d-m, $J_{7,8}$ 9.9, C⁷-H), 5.32 (1 H, t, J 8.1, C³-H), 5.30 (1 H, d, $J_{8,7}$ 10.0, C⁸-H), 5.30 (1 H, t, J 8.5, C⁴-H), 5.15 (1 H, dd, $J_{2,3}$ 8.1, $J_{2,1}$ 7.5, C²-H), 4.95 (1 H, d, $J_{1,2}$ 7.5, C¹-H), 4.91 (1 H, d, $J_{5,6}$ 5.8, C⁵-H), 4.31 (1 H, dd, $J_{6,5}$ 5.5, $J_{6,7}$ 2.0, C⁶-H), 4.14 (1 H, d, J 9.0, C⁵-H), 3.73 (3 H, s, CO₂Me), 3.35 (1 H, m, C⁹-H), 3.05 (1 H, d, $J_{\beta:\alpha}$ 18.8, C¹⁰-H _{β}), 2.44 (3 H, s, N-CH₃), 2.3-2.7 (7 H, m, C¹⁴-H, C¹⁶-H_{eq}, C¹⁶-H_{ax}, C¹⁰-H _{α} , 3x OC(O)CH(CH₃)₂), 2.04 (1 H, td, $J_{\text{gem};15,16\text{ax}}$ 12.0, $J_{15,16\text{eq}}$ 5.0, C¹⁵-H_{ax}), 1.92 (1 H, d(brd), J_{gem} 12.0, C¹⁵-H_{eq});

m/z (FAB) 728 (M⁺+H).

64. Synthesis of morphine-6-glucuronide **40**

3-acetylmorphine-6-methyl(2,3,4-tri-*O*-isobutanoylglucopyranosyl) uronate **95** (40mg, 0.055mmol) was dissolved in a solution of sodium hydroxide (23.5mg, 10 eq) in water (0.47ml) and methanol (2ml) and stood for 1 hour. T.l.c. analysis (mobile phase = 80% methanol/chloroform) indicated complete conversion to a new compound, R_F = 0.25. Acetic acid (0.54ml) was added and the solution was refrigerated for 2 days. A small amount (<5mg) colourless solid had crystallised out. This was collected by filtration but was later shown to contain no opioid material. The filtrate was treated twice with Amberlite IRC-50S ion-exchange resin and concentrated *in vacuo* to an off-white solid (10mg). This was shown by n.m.r. to contain target product but was also shown to be impure with inorganic salts.

δ_H consistent with previous products **40**

Elemental analysis gave low values.

65. Synthesis of DL-7-oxabicyclo[2.2.1]hept-5-ene-2-methylcarboxylate **101**

A mixture of furan (76g, 1.1mol), methyl acrylate (80g, 83ml, 0.9mol) and zinc iodide (32g, 0.1mol) was made up and stored at 4°C. After 2 days, t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated slight conversion. The mixture was stored at 20°C for 4 days after which, t.l.c. analysis indicated almost complete

conversion. The solution was diluted with ethyl acetate (1l) and washed with 0.1M sodium thiosulfate (700ml), dried over sodium sulfate and concentrated *in vacuo* to an oil which was flash chromatographed (mobile phase = ethyl acetate) to afford a colourless oil (53.2g, 35%). Shown to be ~2:1 *endo:exo* adduct mixture.

δ_{H} 6.44 (0.7 H, m, *exo* H-2, H-3), 6.36 (0.65 H, d, $J_{2,3}$ 6.0, *endo* H-2), 6.21 (0.65 H, d, $J_{3,2}$ 6.0, *endo* H-3), 5.14 (1 H, s(brd), H-1), 5.05 (0.35 H, s, *exo* H-4), 5.00 (0.65 H, s, *endo* H-4), 3.71 (1.05 H, s, *exo* CO₂Me), 3.62 (1.95 H, s, *endo* CO₂Me), 3.09 (0.65 H, s, *endo* H-6), 2.41 (0.35 H, s, *exo* H-6), 2.1 (1 H, m, H-5_{eq}), 1.6 (1 H, m, H-5_{ax}).

66. Attempted synthesis of DL-2-*exo*-bromo-4,8-dioxatricyclo[4.2.1.0]nonan-5-one

102

A solution (A) of DL-7-oxabicyclo[2.2.1]hept-5-ene-2-methylcarboxylate **101** (1.75g, 11.4mmol) in acetic acid (10ml) was made up. Meanwhile, a solution of silver acetate (3.6g, 1.9 eq) and bromine (1.73g, 0.56ml, 0.95 eq) in acetic acid (40ml) was stirred for 10 minutes before solution (A) was added and stirred for 1 hour. A solution of water (0.205ml, 1.0 eq) in acetic acid (5ml) was added and the mixture was stirred at 100°C, monitoring by t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether). After 5 hours, no conversion was indicated but slow epimerisation had occurred, giving a stronger spot for the *exo* compound.

67. Synthesis of DL-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid **99**

A solution of DL-7-oxabicyclo[2.2.1]hept-5-ene-2-methylcarboxylate **101** (1.4g, 9.1mmol) and lithium hydroxide monohydrate (760mg, 2.0 eq) in water/methanol 1:2 (20ml) was made up and stirred. After 4 hours, t.l.c. analysis (mobile phase = 40% ethyl acetate/petroleum ether) indicated complete conversion. The solution was concentrated *in vacuo* to an oil to which water was added, acidified with 0.1M potassium hydrogen sulfate, and extracted into ethyl acetate (5x50ml), dried over sodium sulfate, and concentrated *in vacuo* to a near colourless oil which crystallised to a yellow solid on vacuum drying (1.19g, 93%).

m.p. 96-98°C (lit. 97-100°C);

δ_{H} 6.46 (0.65 H, dd, $J_{2,3}$ 5.9, $J_{2,1}$ 1.7, *endo* H-2), 6.42 (0.35 H, dd, $J_{2,3}$ 5.8, $J_{2,1}$ 1.7, *exo* H-2), 6.36 (0.35 H, dd, $J_{3,2}$ 5.9, $J_{3,4}$ 1.7, *exo* H-3), 6.30 (0.65 H, dd, $J_{3,2}$ 5.9, $J_{3,4}$ 1.5, *endo* H-3), 5.25 (0.35 H, dd, $J_{1,2}$ 1.5, $J_{1,3}$ 0.5, *exo* H-1), 5.20 (0.65 H, ddd, $J_{1,6eq}$ 4.8, $J_{1,2}$ 1.6, $J_{1,3}$ 0.6, *endo* H-1), 5.11 (0.35 H, d, $J_{4,5eq}$ 4.8, *exo* H-4), 5.05 (0.65 H, d, $J_{4,5eq}$ 4.8, *endo* H-4), 3.17 (0.65 H, ddd, $J_{6,5eq}$ 9.3, $J_{6,5ax}$ 5.0, $J_{6,1}$ 4.8, *endo* H-6), 2.47 (0.35 H, dd, $J_{6,5ax}$ 8.5, $J_{6,5eq}$ 4.0, *exo* H-6), 2.15 (0.35 H, ddd, J_{gem} 11.5, $J_{5,4}$ 4.8, $J_{5,6}$ 4.0, *exo* H-5_{eq}), 2.15 (0.65 H, ddd, J_{gem} 11.5, $J_{5,6}$ 9.3, $J_{5,4}$ 4.8, *endo* H-5_{eq}), 1.60 (0.35 H, dd, J_{gem} 11.5, $J_{5,6}$ 8.5, *exo* H-5_{ax}), 1.57 (0.65 H, dd, J_{gem} 11.5, $J_{5,6}$ 5.0, *endo* H-5_{ax}).

68. Synthesis of DL-2-*exo*-bromo-4,8-dioxatricyclo[4.2.1.0]nonan-5-one **102**

i) A solution of DL-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid **99** (600mg, 4.2mmol) and sodium hydrogen carbonate (415mg, 1.2 eq) in water (15ml) was stirred and bromine (820mg, 0.26ml, 1.2 eq) was added dropwise. The mixture was stirred and monitored by t.l.c. (mobile phase = 40% ethyl acetate/petroleum ether) which partial conversion after 1 hour with no improvement after 16 hours. The mixture was filtered, basified with saturated sodium hydrogen carbonate, and extracted into ethyl acetate (2x 50ml), dried over sodium sulfate, and concentrated *in vacuo* to a colourless crystalline solid (470mg, 55%).

δ_{H} 5.43 (1 H, t, $J_{1,2;1,6}$ 4.8, H-1), 4.97 (1 H, d, $J_{2,1}$ 4.8, H-2), 4.78 (1 H, d, $J_{4,5eq}$ 5.0, H-4), 3.95 (1 H, s, H-3), 2.77 (1 H, ddd, $J_{6,5eq}$ 11.0, $J_{6,1}$ 5.0, $J_{6,5ax}$ 2.0, H-6), 2.32 (1 H, dd, J_{gem} 14.0, $J_{5,6}$ 11.0, $J_{5,4}$ 5.3, H-5_{eq}), 2.11 (1 H, dd, J_{gem} 14.0, $J_{5,6}$ 2.0, H-5_{ax}).

ii) A solution of DL-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid **99** (6000mg, 4.2mmol) and sodium hydroxide (200mg, 1.2 eq) in water (15ml) was stirred and bromine (820mg, 0.26ml, 1.2 eq) was added dropwise. The mixture was stirred and monitored by t.l.c. (mobile phase = 40% ethyl acetate/petroleum ether) which partial conversion after 1 hour with no improvement after 16 hours. The solution was shown to be acidic so a further portion (1.2 eq) sodium hydroxide was added and the reaction was continued. After 2 hours, t.l.c. analysis indicated further conversion but starting material remained. The mixture was extracted into ethyl acetate (3x 50ml), dried over

sodium sulfate, and concentrated *in vacuo* to a colourless solid (448mg, 48%). Data consistent with above.

69. Synthesis of DL-(1,3,5/2,4)-2,3-diacetoxy-4,5-dibromocyclohexane-1-carboxylic acid **103**

A solution of DL-2-*exo*-bromo-4,8-dioxatricyclo[4.2.1.0]nonan-5-one **102** (1.6g, 7.0mmol) in 20% hydrogen bromide in acetic acid (5ml) was sealed in a thick walled glass tube and heated at 80°C for 2 days. The solution was poured onto ice-water and the resulting precipitate was filtered as a grey solid which was recrystallised from ethanol as a mixture of black solid and colourless prisms (0.5g), but this was shown by n.m.r. and t.l.c. analyses as containing only starting material. The filtrate was concentrated *in vacuo* and crystallised from ether as colourless needles (235mg, 8.4%).

m.p. 202-4°C (lit. 206-7°C);

δ_{H} (DMSO) 1.99 (3 H, s, OAc), 1.89 (3 H, s, OAc).

70. Synthesis of methyl DL-(1,3,5/2,4)-2,3-diacetoxy-4,5-dibromocyclohexane-1-carboxylate **104**

A solution of DL-(1,3,5/2,4)-2,3-diacetoxy-4,5-dibromocyclohexane-1-carboxylic acid **103** (184mg, 0.46mmol) in methanol (3.7ml) was stirred at 0°C and acetyl chloride (61mg, 0.055ml, 1.7 eq) was added dropwise. The solution was boiled for 2 hours and monitored by t.l.c. (mobile phase = 40% ethyl acetate/petroleum ether) which showed 3 compounds present. The reaction was continued for a further 2 hours but no change was observed. The solution was neutralised with solid sodium hydrogen carbonate and concentrated *in vacuo* to an oil to which was added acetic acid (1ml) and pyridine (1ml) and the solution was stirred for 3 days. T.l.c. analysis showed conversion to one product. The solution was diluted with ethyl acetate (50ml), washed with 1M hydrochloric acid (50ml) and subsequently saturated sodium hydrogen carbonate, dried over sodium sulfate and concentrated *in vacuo* to a colourless solid (117mg, 66%).

m.p. 180-2°C (lit. 182.5-184.5°C):

δ_{H} 3.69 (3 H, s, CO₂Me), 2.09 (3 H, s, OAc), 1.99 (3 H, s, OAc);

71. Attempted synthesis of 3-acetylmorphine-6-(2-hydroxycyclohexyl)ether

A solution of 3-acetylmorphine **47** (177mg, 0.54mmol), cyclohexene oxide (53mg, 1.0 eq) and magnesium perchlorate (120mg, 1.0 eq) in acetonitrile (2ml) was boiled for 8

hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated complete conversion to a new compound, $R_F = 0.15$ and 2 other minor by-products, $R_F = 0.25$ and 0.3. The mixture was concentrated *in vacuo* to an oil which was flash chromatographed to afford the main product (72mg). Shown to be morphine.

72. Synthesis of dibutyltin bis(dibutyl phosphate) (OPC)

A solution of dibutyltin oxide (2.5g, 10mmol) and dibutylphosphate (4.2g, 4.0ml, 2 eq) in benzene (200ml) was boiled under Dean and Stark conditions. After 12 hours, the benzene was evaporated *in vacuo* leaving a colourless solid which was dissolved in hot chloroform-hexane. The impurities were filtered off and the filtrate was left to cool. No crystals had formed so the solution was concentrated *in vacuo* leaving a colourless solid (4.15g, 63%).

73. Attempted synthesis of 3-'butyldimethylsilylmorphine-6-(2-hydroxycyclohexyl)ether

i) A solution of 3-'butyldimethylsilylmorphine **57** (200mg, 0.5mmol), cyclohexene oxide (49mg, 1.0 eq) and OPC (100mg, 0.3 eq) in petroleum ether (5ml) was boiled

for 4 days. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction with all 3 starting materials unaffected.

ii) A solution of 3-'butyldimethylsilylmorphine **57** (200mg, 0.5mmol), cyclohexene oxide (49mg, 1.0 eq) and OPC (100mg, 0.3 eq) in petroleum ether (5ml) was boiled for 4 days. 3-'butyldimethylsilyl chloride (75mg, 1.0 eq) was added and the solution was boiled for a further 8 hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction with all 3 starting materials unaffected.

iii) A solution of 3-'butyldimethylsilylmorphine **57** (200mg, 0.5mmol), cyclohexene oxide (49mg, 1.0 eq) and OPC (425mg, 1.3 eq) in petroleum ether (5ml) was boiled for 2 days. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction with all 3 starting materials unaffected.

iv) A solution of 3-'butyldimethylsilylmorphine **57** (200mg, 0.5mmol), cyclohexene oxide (49mg, 1.0 eq) and OPC (425mg, 1.3 eq) in petroleum ether (5ml) was boiled for 2 days. 3-'butyldimethylsilyl chloride (75mg, 1.0 eq) was added and the solution was boiled for a further 8 hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction with all 3 starting materials unaffected.

v) A solution of 3-*t*-butyldimethylsilylmorphine **57** (200mg, 0.5mmol), cyclohexene oxide (49mg, 1.0 eq) and sodium hydride (13mg, 1.1 eq) in THF (5ml) was stirred for 2 hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated no reaction. The mixture was boiled for 6 hours, after which, t.l.c. analysis indicated ~80% to a new compound, $R_F = 0.15$. The solution was quenched with aqueous acetic acid, washed with ethyl acetate, basified with saturated sodium hydrogen carbonate, and extracted into ethyl acetate (7x), dried over sodium sulfate and concentrated *in vacuo* to a dark solid. Crystallisation from ether gave an off-white solid which was shown by n.m.r. to be morphine (78mg, 55%).

74. Attempted synthesis of 3-*t*-butyldimethylsilylmorphine-6-cyclohexylether

A solution of cyclohexanol (50mg, 0.5mmol) and pyridine (60mg, 1.5 eq) in DCM (2ml) was stirred at -23°C, triflic anhydride (140mg, 0.084ml, 1.0 eq) was added dropwise and the solution was stirred for 1 hour. 3-*t*-butyldimethylsilylmorphine **57** (200mg, 0.5mmol) in DCM (0.5ml) was added dropwise and the solution turned red. After warming to 20°C the colour changed to light brown and t.l.c. analysis (mobile phase = 10% methanol/chloroform) revealed the presence of several compounds. After a further 20 minutes, the solution had turned dark and t.l.c indicated conversion to 1 main product, $R_F = 0.15$. The solution was quenched with aqueous acetic acid, washed with ethyl acetate, basified with saturated sodium hydrogen carbonate, and

extracted into ethyl acetate (6x), dried over sodium sulfate and concentrated *in vacuo* to a red oil which was shown to contain only morphine (80mg, 56%).

δ_H consistent with that of morphine.

75. Attempted synthesis of codeine-6-cyclohexylether

i) A solution of cyclohexanol (60mg, 0.6mmol) and pyridine (142mg, 3.0 eq) in DCM (2ml) was stirred at -23°C, triflic anhydride (0.1ml, 1.0 eq) was added dropwise and the solution was stirred for 1 hour. Codeine (150mg, 0.5mmol) in DCM (0.5ml) was added dropwise. The solution was warmed to 20°C and t.l.c (mobile phase = 10% methanol/chloroform) indicated conversion to 1 main product, $R_F = 0.25$. The solution was concentrated *in vacuo*, diluted with ethyl acetate and extracted into ice-cold 1M hydrochloric acid. This was basified with saturated sodium hydrogen carbonate and the product was extracted into ethyl acetate (5x), dried over sodium sulfate and concentrated *in vacuo* to a colourless solid which was shown to contain only codeine (49mg, 32%). Different R_F assumed to be due to triflate salt.

ii) A solution of codeine (300mg, 1.0mmol), cyclohexyl bromide (325mg, 0.245ml, 2.0 eq) and silver carbonate on celite (3.0g, 5 eq) in toluene (5ml) was boiled for 8 hours. T.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated partial conversion to a new compound, $R_F = 0.5$. The mixture was cooled, filtered (washing with

chloroform), and the filtrate was concentrated *in vacuo* to a dark oil. This was taken up in ether and extracted into ice-cold 1M hydrochloric acid, basified with sodium hydrogen carbonate and extracted into chloroform. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo* to a light brown solid (110mg). Product was shown by n.m.r. to contain no cyclohexyl group and was consistent with the by-product from previous reactions of codeine using silver carbonate on celite.

iii) A solution of codeine (150mg, 0.5mmol) and sodium hydride (29mg, 2.4 eq) in THF (5ml) was stirred for 10 minutes before cyclohexyl bromide (163mg, 0.12ml, 2.0 eq) was added dropwise. After 2 hours, t.l.c. analysis (mobile phase = 10% methanol/chloroform) showed no reaction so a further portion (2.5 eq) sodium hydride was added and the reaction was continued for 12 hours, during which time the solution turned red but t.l.c. analysis still indicated no conversion. The solution was boiled for 5 hours, but t.l.c. analysis still indicated no conversion.

76. Attempted synthesis of α -bromocodide (6 β -bromocodide) 107

A solution of phosphorus pentabromide (2.16g, 5.0mmol) in chloroform (5ml) was made up at 0°C and codeine (900mg, 3.0mmol) was added in portions. The solution was stirred at 20°C for 5 hours and t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated complete conversion. The solution was quenched with

water followed by saturated sodium hydrogen carbonate and stirred with heating until the red colouration disappeared. Extraction into ethyl acetate and concentration *in vacuo* gave an oil which was flash chromatographed to afford a colourless solid which was shown to be the dibromide (920mg, 69%) mostly as 1,6-dibromocodide.

m/z (C.I.) 442 ($M^+ + H$), 360, 362 ($M^+ + H - Br$);

δ_H 6.86 (1 H, s, C^2-H), 6.05 (1 H, ddd, $J_{7,8}$ 11.0, $J_{7,6}$ 6.5, $J_{7,14}$ 3.0, C^7-H), 5.63 (1 H, dd, $J_{8,7}$ 11.0, $J_{8,14}$ 2.5, C^8-H), 5.21 (1 H, s, C^5-H), 4.66 (1 H, d, $J_{6,7}$ 6.0, C^6-H), 3.84 (3 H, s, OMe), 3.39 (1 H, dd, $J_{9,10\alpha}$ 6.0, $J_{9,14}$ 3.5, C^9-H), 3.08 (1 H, d, J_{gem} 15.8, $C^{10}-H_\beta$), 2.62 (1 H, dd, J_{gem} 12.0, $J_{16,15}$ 5.0, $C^{16}-H_{eq}$), 2.44 (3 H, s, NMe), 2.3-2.5 (3 H, m, $C^{14}-H$, $C^{16}-H_{ax}$, $C^{10}-H_\alpha$), 1.86 (1 H, d(brd), J_{gem} 12.0, $C^{15}-H_{eq}$).

77. Synthesis of α -bromocodide (6 β -bromocodide) **107**

A solution of codeine (315mg, 1.15mmol) and phosphorus tribromide (476mg, 0.17ml, 1.5 eq) in DCM (10ml) was stirred for 12 hours, after which, t.l.c. analysis (mobile phase = 10% methanol/chloroform) indicated conversion to 3 new compounds, R_F = 0.1, 0.80, and 0.82. The solution was neutralised with saturated sodium hydrogen carbonate, extracted into ethyl acetate and concentration *in vacuo* gave an oil which was flash chromatographed to afford oils, β -bromocodide (8 β -bromocodide) **108** (13mg, 3%), and α -bromocodide (6 β -bromocodide) **107** (47mg, 11%).

107:

δ_{H} 6.67 (1 H, d, J 8.2, C²-H), 6.57 (1 H, d, J 8.2, C¹-H), 6.02 (1 H, ddd, $J_{7,8}$ 9.5, $J_{7,6}$ 6.0, $J_{7,14}$ 3.0, C⁷-H), 5.65 (1 H, dd, $J_{8,7}$ 9.5, $J_{8,14}$ 2.0, C⁸-H), 5.20 (1 H, s, C⁵-H), 4.66 (1 H, d, $J_{6,7}$ 6.0, C⁶-H), 3.84 (3 H, s, OMe), 3.39 (1 H, dd, $J_{9,10\alpha}$ 6.0, $J_{9,14}$ 3.5, C⁹-H), 3.08 (1 H, d, J_{gem} 15.8, C¹⁰-H $_{\beta}$), 2.62 (1 H, dd, J_{gem} 12.0, $J_{16,15}$ 5.0, C¹⁶-H $_{\text{eq}}$), 2.44 (3 H, s, NMe), 2.3-2.5 (3 H, m, C¹⁴-H, C¹⁶-H $_{\text{ax}}$, C¹⁰-H $_{\alpha}$), 1.86 (1 H, d(brd), J_{gem} 12.0, C¹⁵-H $_{\text{eq}}$);

m/z (FAB) 360 ($M^+ + H$).

108:

δ_{H} 6.72 (1 H, d, J 8.2, C²-H), 6.65 (1 H, d, J 8.2, C¹-H), 6.05 (1 H, dd, $J_{7,6}$ 10.4, $J_{7,8}$ 1.5, C⁷-H), 5.69 (1 H, dt, $J_{6,7}$ 10.4, $J_{6,5;6,8}$ 3.3, C⁶-H), 5.04 (1 H, d, $J_{5,6}$ 3.3, C⁵-H), 4.13 (1 H, ddd, $J_{8,14}$ 10.1, $J_{8,6}$ 3.4, $J_{8,7}$ 1.5, C⁸-H), 3.84 (3 H, s, NMe), 3.57 (1 H, dd, $J_{9,10\alpha}$ 6.0, $J_{9,14}$ 2.7, C⁹-H), 3.08 (1 H, d, J_{gem} 18.9, C¹⁰-H $_{\beta}$), 2.73 (1 H, dd, $J_{14,8}$ 9.9, $J_{14,9}$ 2.7, C¹⁴-H), 2.45 (3 H, s, NMe), 2.5 (1 H, m, C¹⁶-H $_{\text{eq}}$), 2.40 (1 H, dd, J_{gem} 18.7, $J_{10,9}$ 6.0, C¹⁰-H $_{\alpha}$), 2.28 (1 H, td, $J_{\text{gem};16,15\text{ax}}$ 12.1, $J_{16,15\text{eq}}$ 3.7, C¹⁶-H $_{\text{ax}}$), 1.94 (1 H, td, $J_{\text{gem};15,16\text{ax}}$ 12.3, $J_{15,16\text{eq}}$ 5.1, C¹⁵-H $_{\text{ax}}$), 1.78 (1 H, ddd, J_{gem} 12.5, $J_{15,16\text{ax}}$ 3.7, $J_{15,16\text{eq}}$ 1.5, C¹⁵-H $_{\text{eq}}$).

D. REFERENCES

1. Foye, W. O., ed. *Principles of Medicinal Chemistry*, 3rd Ed., p. 144, Lea and Febiger, Philadelphia and London 1989
2. Foye, W. O., ed. *Principles of Medicinal Chemistry*, 3rd Ed., p. 239, Lea and Febiger, Philadelphia and London 1989
3. Chau-Pham, T. T.; *Drug Metab. rev.* 1978, **7**, 255
4. Snyder, S. H.; *Sci. Am.* 1977, **236**, 44
5. Snyder, S. H.; *Chem. Eng. News* 1977, **55**, 26
6. Simon, E. J.; Hiller, J. M.; *Ann. Rev. Pharmacol. Toxicol.* 1978, **18**, 371
7. Goldstein, A.; Lowney, L.I.; Pal, B.K.; *Proc. Natl. Acad. Sci. U.S.A.* 1971, **68**, 1742
8. Goldstein, A. *in: Biological Behavioural Approaches To Drug Dependence* (H. Cappel & A. E. LeBlanc, Eds) Addiction Research Foundation, Toronto 1973
9. "The Opiate Narcotics", *Life Sci.* 1975, **16**, (12), 1-
10. Hughes, J.; Smith, T. W.; Kosterlitz, H. W.; Fothergill, L. A.; Morgan, B. A.; Morris, H. R.; *Nature* 1975, **258**, 577
11. Hughes, J.; Smith, T. W.; Fothergill, L. A.; Morgan, B. A.; *Life Sci.* 1975, **16**, 1753
12. Taber, R.; Frederickson, R. C. A.; Smithwick, E. L.; Schuman, E. L.; Gesellchen, P. D.; *Psychopharmacol. Bull.* 1981, **17**, 106
13. Goldstein, A.; *Sci.* 1976, **193**, 1081
14. Comb, M.; Seæberg, P. H.; Adelman, J.; Eiden, L.; Herbert, E.; *Nature* 1982, **295**, 663

15. Noda, M.; Furutani, Y.; Takahashi, H.; Toyosato, M.; Hirose, T.; Kayonna, S.; Nakanishi, S.; Numa, S.; *Nature* 1982, **295**, 202
16. Smyth, D.G.; *Br. Med. Bull.* 39, **25**, 1983
17. Martin, W. R., Eades, C. G.; Thompson, J. A.; Huppler, R. E.; *J. Pharmacol. Exp. Ther.* 1976, **197**, 517
18. Gilbert, P. E.; Martin, W. R.; *J. Pharmacol. Exp. Ther.* 1976, **198**, 66
19. Lord, J. A. H.; Waterfield, A. A.; Hughes, J.; Kosterlitz, H.W.; *Opiates & Endogenous Opioid Peptides*, Kosterlitz Ed. Elsevier, Amsterdam 1976, 275
20. Knoll, J.; Iblis, P.; Medzihradszky, K.; *J. Pharm. Pharmacol.* 1978, **30**, 394
21. Wüster, M.; Schulz, R.; Herz, A.; *Neurosci. Lett.* 1979, **15**, 193
22. Wüster, M.; Schulz, R.; Herz, A.; *Eur. J. Pharmacol.* 1980, **62**, 235
23. DeVries, T. J.; Hogenboom, F.; Mulder, A. H.; Schoffemeer, A. N. M.; *Dev, Brain Res.* 1990, **54**, 63
24. Werling, L. L.; Frattali, A.; Portoghese, P. S.; Takemori, A. E.; Cox, B. M.; *J. Pharmacol. Exp. Ther.* 1988, **246**, 282
25. Mulder, A. H.; Wardeh, G.; Hogenboom, F.; Frankhuyen, A. L.; *Neuropeptides* 1989, **14**, 99
26. Paterson, S. J.; Robson, L. E.; Kosterlitz, H. W.; *Br. Med. Bull.* 1983, **39**, 31
27. Rónai, A. Z.; Székely, J. I.; Berzétei, I.; Miglécz, E.; Bajusz, S.; *Biochem. Biophys. Res. Commun.* 1979, **91**, 1239
28. Soós, J.; Berzétei, I.; Bajusz, S.; Rónai, A. Z.; *Life Sci.* 1980, **27**, 129
29. Pasternak, G. W.; Wood, P. J.; *Life Sci.* 1986, **38**, 1889
30. Moskowitz, A. S.; Goodman, R. R.; *Brain Res.* 1985, **360**, 108
31. Kosterlitz, H. W.; Waterfield, A. A.; *Ann. Rev. Pharmacol.* 1975, **15**, 29

32. Lord, J. A. H.; Waterfield, A. A.; Hughes, J.; Kosterlitz, H. W.; *Nature* 1977, **267**, 495
33. Martin, W. R.; Eades, C. G.; Thompson, W. O.; Thompson, J. A.; Flanary, H. G.; *J. Pharmacol. Exp. Ther.* 1974, **189**, 759
34. Frenk, H.; Urca, G.; Liebeskind, J. C.; *Brain Res.* 1978, **147**, 327
35. Urca, G.; Frenk, H.; Liebeskind, J. C.; *Science* 1978, **197**, 83
36. Rónai, A. Z.; Berzétei, I.; Bajusz, S.; *Eur. J. Pharmacol.* 1977, **45**, 393
37. Shaw, J. S.; Turnbull, M. J.; *Eur. J. Pharmacol.* 1978, **49**, 313
38. Waterfield, A. A.; Smockum, R. W. J.; Hughes, J.; Kosterlitz, H. W.; Henderson, G.; *Eur. J. Pharmacol.* 1977, **43**, 107
39. Schulz, R.; Wüster, M.; Krenss, H.; Herz, A.; *Nature* 1980, **285**, 242
40. Zieglgänsberger, W.; Fry, J. P.; Lambert, L. A.; *Endogenous & Exogenous Opiate Agonists and Antagonists* (E. L. Way, Ed), p. 139, Pergamon Press, N. Y. 1979
41. Schoffeleer, A. N. M.; Wardeh, G.; Hogenboom, F.; Mulder, A. H.; *J. Pharmacol. Exp. Ther.* 1991, **258**, 237
42. Gulland, J. M.; Robinson, R.; *J. Chem. Soc.* 1923, 980
43. Winter, C. A.; in: *Analgetics* (G. deStevens, ed.), Academic Press, New York 1965
44. Lewis, J. W.; Bentley, K. W.; Cowan, A.; *Ann. Rev. Pharmacol. Toxicol.* 1971, **11**, 241
45. Kosterlitz, H. W.; Collier, H. O. J.; Villarreal, J. E., eds., *Agonist and Antagonist Actions of Narcotic Analgesic Drugs*, University Park Press, Baltimore 1973

46. Martin W. R.; Sloan J. W.; in: *Handbook of Experimental Pharmacology* (W. R. Martin, ed), Vol. 45, p.43, Springer-Verlag, Berlin 1977
47. Adler, M. W.; Manara, L.; Samanin, R., eds., *Factors Affecting the Action of Narcotics*, Raven Press, New York 1978
48. Jaffe, J. H.; Martin, W. R.; in: *The Pharmacological Basis of Therapeutics* (A. G. Gilman, L. S. Goodman, A. Gilman, eds.), 6th ed., p. 494, Macmillan, New York 1980
49. Jaffe, J. H.; in: *The Pharmacological Basis of Therapeutics* (A. G. Gilman, L. S. Goodman, A. Gilman, eds.), 6th ed., p. 535, Macmillan, New York 1980
50. Wright, C. R. A.; *J. Chem. Soc.* 1874, **27**, 1031
51. Gates, M.; Tschudi, G.; *J. Am. Chem. Soc.* 1952, **74**, 1109
52. Gates, M.; Tschudi, G.; *J. Am. Chem. Soc.* 1956, **78**, 1380
53. Kametani, T.; in: *The Total Synthesis Of Natural Products* (J. ApSimon, Ed.) Vol 3. Wiley, N. Y. 1977
54. Bentley, K. W.; Hardy, D. G.; *Proc. Chem. Soc.* 1963, 220
55. Blane, G. F.; Boura, A. L. A.; Fitzgerald, A. E.; Lister, R. E.; *Br. J. Pharmacol.* 1967, **30**, 11
56. Downing, S. N.; Leary, W. P.; White, E. S.; *Br. J. Anaesthesia* 1977, **47**, 251
57. Alder, T. K.; *J. Pharmacol. Exp. Ther.* 1963, **140**, 155
58. Kamm, J. J.; Bastone, V. B.; Mohacsi, E.; Vane, F. M.; *Xenobiotica* 1971, **1**, 273
59. Mohacsi, B.; Leimgruber, W.; Barnth, H.; *J. Med. Chem.* 1982, **25**, 1264
60. Shimomura, K.; Kamata, O.; Ueki, S.; Ida, S.; Oguri, K. *et al.*; *Tohoku J. Exp. Med.* 1971, **105**, 45

61. Mori, M.; Ogeri, K.; Yoshimura, H.; Kamata, O.; Veki, S.; *Life Sci.* 1972, **11**, 525
62. Way, E. L.; Kemp, J. W.; Young, J. M.; Grasetti, D. R.; *J. Pharmacol. Exp. Ther.* 1960, **129**, 144
63. Casy, A. F.; Parfitt, R. T., eds. *Opioid Analgesics* p. 11, Plenum Press, New York and London 1986
64. Mackay, M.; Hodgkin, D. C.; *J. Chem. Soc.* 1955, 3261
65. Brown, C. E.; Roerig, S. J.; Fujimoto, J. M.; Burger, V. T.; *J. Chem. Soc. Chem. Commun.* 1983, 1506
66. Kugita, H.; Takeda, M.; *Chem. & Ind. (Lond)* 1964, 2099
67. Kugita, H.; Takeda, M.; *Chem. Pharm. Bull.* 1965, **13**, 1422
68. Iigima, I.; Minamikawa, J.; Jacobson, A. E.; Brossi, A.; Rice, K. C.; *J. Org. Chem.* 1978, **43**, 1462
69. Beckett, A. H.; Casy, A. F.; *J. Pharm. Pharmacol.* 1954, **6**, 986
70. Eddy, N. B.; *Chem. & Ind. (Lond)* 1959, 1462
71. Beckett, A. H.; Casy, A. F.; Harper, N. J.; *J. Pharm. Pharmacol.* 1956, **8**, 874
72. Clark, R. L.; Pessolano, A. A.; Weijlard, J.; Pfister, K.; *J. Am. Chem. Soc.* 1953, **75**, 4963
73. Winter, C. A.; Orahovats, P. D.; Lehman, E. G.; *Arch. Int. Pharmacodyn.* 1957, **10**, 186
74. Pohl, J.; *Zeitschr. Exp. Pathol. Therap.* 1915, **17**, 370
75. McCawley, W. L.; Hart, E. R.; Marsh, D. F.; *J. Am. Chem. Soc.* 1941, **63**, 314
76. Echenhoff, J. E.; Elder, J. D.; *Am. J. Med. Sci.* 1952, **223**, 191

77. Costa, E.; Greengard, P., Eds. *Adv. in Biochem. Pharmacol.* Vol. 8 *Narcotic Antagonists* Raven Press, N. Y. 1973
78. Casy, A. F.; Parfitt, R. T., eds. *Opioid Analgesics* Ch. 12, Plenum Press, New York and London 1986
79. Casy, A. F.; Parfitt, R. T., eds. *Opioid Analgesics* p. 31, Plenum Press, New York and London 1986
80. Gates, M.; Montzka, T.; *J. Med. Chem.* 1964, **7**, 127
81. Way, E. L.; Adler, T. K.; *The Biological Disposition Of Morphine And Its Surrogates* W.H.O. Geneva 1962
82. Lemberger, L.; Rubin, A.; *Physiological Disposition Of Drugs* Ch. 5 Spectrum Publications, N. Y. 1976
83. Yeh, S. Y.; *J. Pharmacol. Exp. Ther.* 1975, **192**, 201
84. Yoshimura, H.; *J. Pharmacobiodyn.* 1980, **3**, S6
85. Casy, A. F.; Parfitt, R. T., eds. *Opioid Analgesics* p. 87-88, Plenum Press, New York and London 1986
86. Inturrisi, C. E; Max, M.; Umans, J.; Schultz, M.; Shin, S.; Foley, K.; Houde, R. D.; *Clin. Pharmacol. Ther.* 1982, **31**, 235
87. Inturrisi, C. E; Schultz, M.; Shin, S.; Umans, J. G.; Angel, L.; Simm, E. J.; *Life Sci.* 1983, **33**, Suppl.1, 773
88. Yeh, S. Y.; McQuinn, R. L.; Gorodetzky, C. W.; *J. Pharm. Sci.* 1977, **66**, 201
89. Dutton, G. J.; in: *Glucuronic Acid - Free And Combined* Academic Press, N. Y. & London 1966
90. Wahlström, A.; Pacifici, G. M.; Lindstrom, B.; Hammar, L.; Rane, A.; *Br. J. Pharmacol.* 1988, **94**, 864

91. Rane, A.; Gawronska-Szklarz, B.; Svensson, J-O.; *J. Pharmacol. Exp. Ther.* 1985, **234**, 761
92. Coughtrie, M. W. H.; Ask, B.; Rane, A.; Burchell, B.; Hume, R.; *Biochem. Pharmacol.* 1989, **38**, 3273
93. Lawrence, A. J.; Michalkiewicz, A.; Morley, J. S.; Mackinnon, K.; Billington, D.; *Biochem. Pharmacol.* 1992, **43**, 2335
94. Yoshimura, H.; Ida, S.; Oguri, K.; Tsukamoto, H.; *Biochem. Pharmacol.* 1973, **22**, 1423
95. Pasternak, G.W.; Bodnar, R.J.; Clark, J.A.; Inturrisi, C.E.; *Life Sci.* 1987, **41**, 2845
96. Paul, D.; Standifer, K.M.; Inturrisi, C.E.; Pasternak, G.W.; *J. Pharmacol. Exp. Ther* 1989, **251**, 477
97. Hanks, G. W.; Aherne, G.W.; Hoskin, P. J.; Turner, P.; Poulain, P.; *Lancet* 2 1987, 723
98. Frances, B.; Cout, R.; Monsarrat, B.; Cros, J.; Zajac, J-M.; *J. Pharmacol. Exp. Ther.* 1992, **262**, 25
99. Goodman, L.S. & Gilman, A. *The Pharmacological Basis Of Therapeutics* 6th Ed Macmillan NY 1980 P.505
100. Peat, S.J.; Hanna, M.H.; Woodham, M.; Knibb, A.A.; Ponte, J.; *Pain* 1991, **45**, 101
101. Osborne, R.; Thompson, P.; Joel, S.; Trew, D.; Patel, N.; Slevin, M.; *Br. J. Clin. Pharmac.* 1992, **34**, 130
102. Russel, R. D.; Leslie, J. B.; Su, Y. F.; Watkins, W. D.; Chang, K. J.; *J. Pharmacol. Exp. Ther.* 1987, **240**, 150

103. Ling, G. S. F.; Spiegel, K.; Lockhart, S. H.; Pasternak, G. W.; *J. Pharmacol. Exp. Ther.* 1985, **232**, 149
104. Pasternak, G. W.; *Biochem. Pharmacol.* 1986, **35**, 361
105. Porecca, F.; Mosberg, H. I.; Omnaas, J. R.; Burks, T. F.; Cowan, A.; *J. Pharmacol. Exp. Ther.* 1987, **240**, 890
106. Gairin, J. E.; Gout, R.; Meunier, J-C.; Cros, J.; *J. Pharmacol. Exp. Ther.* 1988, **245**, 995
107. Millan, M. J.; *Trends Pharmacol. Sci.* 1990, **11**, 70
108. Svensson, J-O.; Rand, A.; Sawe, J.; Sjoqvist, F.; *J. Chromatog.* 1982, **230**, 427
109. Moore, R. A.; Sear, J.; Baldwin, D. *et al.*; *Clin. Pharmacol. Ther.* 1984, **35**, 641
110. Joel, S. P.; Osborne, R. J.; Nixon, N. S.; Slevin, M. L.; *The Lancet* 1985, 1099
111. Pasternak, G. W.; *Clin. Neuropharm.* 1993, **16**, 1
112. Osborne, R. J.; Joel, S. P.; Slevin, M. L.; *Br. Med. J.* 1986, **292**, 1548
113. Portenoy, R. K.; Foley, K. M. *et al.*; *Pain* 1991, **47**, 13
114. Schneider, J. J.; Ravenscroft, P. J.; Cavenagh, J. D.; Brown, A. M.; Bradley, J. P.; *Br. J. Clin. Pharm.* 1992, **34**, 431
115. Smith, M.T.; Watt, J.A.; Cramond, T.; *Life Sci.* 1990, **47**, 579
116. Gong, Q-L.; Hedner, J.; Bjorkman, R.; Hedner, T.; *Pain* 1992, **48**, 249
117. Suzuki, N.; Kalso, E.; Rosenberg, P. H.; *Eur. J. Pharmacol.* 1993, **249**, 247
118. Yoshimura, H.; Oguri, K.; Tsukamoto, H.; *Chem. Pharm. Bull.* 1968, **16**, 2114
119. Carrupt, P. A.; Testa, B.; Bechalany, A.; El Tayar, N.; Descas, P.; Perrissoud, D.; *J. Med. Chem.* 1991, **34**, 1272
120. Bowering, W.D.S; Timell, T. E.; *J. Am. Chem. Soc.* 1960, **82**, 2827
121. Bollenback, G. N. *et al.*; *J. Am. Chem. Soc.* 1955, **77**, 3310

122. Wolfrom, M. L.; Lineback, D. R.; in 'Methods in Carbohydrate Chemistry' Vol 2
p. 341, 1963
123. Isbell, H. S.; *Ann. Rev. Biochem.* 1940, **9**, 65
124. Mitsunobu, O.; *Synthesis* 1981, 1
125. Still, C.; *J. Am. Chem. Soc.* 1985, **107**, 6372
126. Szarek, *et al.*; *Carbohydrate Res.* 1977, **57**, C13
127. Tsunoda, T.; Yamamiya, Y.; Ito, S.; *Tet. Lett.* 1993, **34**, 1639
128. Schmidt, R. R.; Behrendt, M.; Toepter, A.; *Synlett* 1990, 694
129. Ferrier, R. J.; Furneaux, R. H.; *Carbohydrate Res.* 1976, **52**, 63
130. Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R.; *Tetrahedron*
1991, **47**, 9985
131. Koide, K.; Ohno, M.; Kobayashi, S.; *Tet. Lett.* 1991, **32**, 7065
132. Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H.; *J. Org. Chem.* 1990, **55**,
6068
133. Schmidt, R. R.; Grundler, G.; *Synthesis* 1981, 885
134. Kovak, P.; Alfoldi, J.; Kosik, M.; *Chem. Zvesti* 1974, **28**, 820
135. Schmidt, R. R.; Rücker, E.; *Tet. Lett.* 1980, **21**, 1421
136. Jung, M. E.; Lyster, M. A.; *J. Org. Chem.* 1977, **42**, 3716
137. Demuyne, M.; De Clercq, P.; Vandewalle, M.; *J. Org. Chem.* 1979, **44**, 4863
138. Van Boeckel, C. A. A. *et al.*; *Rec. Trav. Chim. Pays-Bas* 1985, **104**, 259
139. Czernecki, S.; Georgoulis, C.; Provelenghiou, C.; *Tet. Lett.* 1976, 3535
140. Kanai, K.; Sakamoto, I.; Ogawa, S.; Suami, T.; *Bull. Chem. Soc. Japan* 1987,
60, 1529
141. Iversen, t.; Bundle, K. R.; *J. Chem. Soc. Chem. Commun.* 1981, 1240

142. Daly, S. M.; Armstrong, R. W.; *Tet. Lett.* 1989, **30**, 5713
143. Corey, E. J.; Venkateswarlu, A.; *J. Am. Chem. Soc.* 1972, **94**, 6190
144. Salford Ultrafine Chemicals and Research Ltd. PCT/GB92/01449 (1993)
145. Helferich, B.; Berger, A.; *Chem. Ber.* 1957, **19**, 1409
146. Plattner, J. J.; Gless, R. D.; Rapoport, H.; *J. Am. Chem. Soc.* 1972, **94**, 8613
147. Prof. G. Buchanan; University of Bath, personal communication.
148. Neilson, T.; Werstiuk, E. S.; *Can. J. Chem.* 1971, **49**, 493
149. Kuhn, R.; Low, J.; Trischmann, H.; *Chem. Ber.* 1957, **90**, 203
150. Iwashige, T.; Saeki, H.; *Chem. Pharm. Bull.* 1967, **15**, 1803
151. Gent, P. A.; Gigg, R.; *J. Chem. Soc. Perkin Trans. I.* 1974, 1839
152. Schmidt, R. R.; Reichrath, M.; Moering, U.; *Tet. Lett.* 1980, **21**, 3561
153. Small, L. F.; Cohen, F. L.; *J. Am. Chem. Soc.* 1931, **53**, 2214
154. Glaudemans, C. P. J.; Fletcher, H. G.; *Methods in Carb. Chem.* 1972, **6**, 373
155. Casparis, P. *et al.*; *Pharm. Acta. Helv.* 1949, **24**, 145
156. Turner, N. J.; Webberley, M. C.; *J. Chem. Soc. Chem. Commun.* 1991, 1349
157. Schneider, G. *et al.*; *Tetrahedron* 1989, **45**, 1355
158. Ranu, B. C.; Basu, M. K.; Sarkar, D. C.; *Synth. Commun.* 1989, **19**, 627
159. Ogawa, S. *et al.*; *Carbohydrate Res.* 1986, **148**, 249
160. Kunstmann, M. P.; Tarbell, D. S.; Autrey, R. L.; *J. Am. Chem. Soc.* 1962, **84**, 4115
161. Brion, F.; *Tet. Lett.* 1982, **23**, 5299
162. Gunstone, F. D.; in: 'Advances In Organic Chemistry: Methods And Results', 1960 Vol. 1, p.p. 103-47, Eds. R. A. Raphael, E. C. Taylor, H. Wynberg; Wiley Interscience, New York.

R. Yavarzadeh: *PhD Thesis*: 1985, University of Bath.

163. Chini, M.; Cretti, P.; Gardelli, C.; Macchia, F.; *Synlett* 1992, 673
164. Otera, J.; Yoshinaga, Y.; Hirakawa, K.; *Tet. Lett.* 1985, **26**, 3219
165. Otera, J.; Niibo, Y.; Tatsumi, N.; Nozaki, H.; *J. Org. Chem.* 1988, **53**, 275
166. Niibo, Y.; Nakata, T.; Otera, J.; Nozaki, H.; *Synlett* 1991, 97
167. Otera, J.; Yano, T.; Kunimoto, E.; Nakata, T.; *Organometallics* 1984, **3**, 426
168. Stang, P. J.; Hanack, M.; Subramanian, L. R.; *Synthesis* 1982, 85
169. Giese, B., ed. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Vol. 5. Pergamon Press, (1986)
170. Kalinin, V. N., *et al.*; *Helv. Chim. Acta* 1994, **77**, 164
171. Schryver, S. B.; Lees, F. H.; *J. Chem. Soc.* 1901, **79**, 563
172. Gates, M.; Shepard, M. S.; *J. Am. Chem. Soc.* 1962, **84**, 4125
173. Carroll, F. I.; Moreland, C. G.; Brine, G. A.; Kepler, J. A.; *J. Org. Chem.* 1976, **41**, 996



A Synthesis of Morphine-6-glucuronide

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Abstract: A practical synthesis of morphine-6-glucuronide from 3-acetylmorphine and methyl 2- α -bromo-3,4,5-tri-*O*-acetylglucuronate is described. Similar syntheses of codeine-6-glucuronide, codeine-6-glucoside and morphine-6-glucoside are also documented

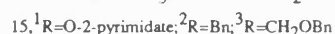
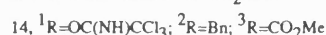
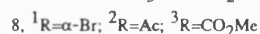
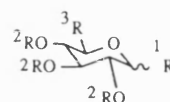
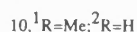
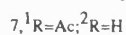
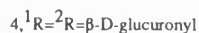
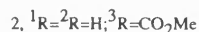
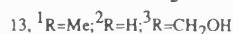
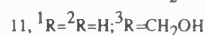
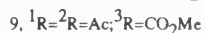
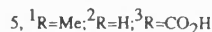
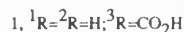
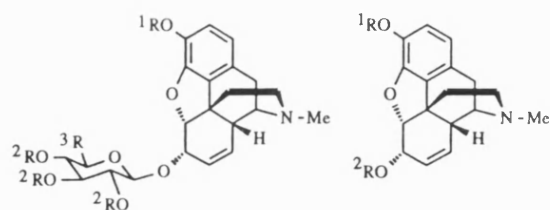
The morphine metabolite morphine-6-glucuronide (M6G, 1) is a more effective and longer lasting analgesic drug than morphine (2) with fewer side effects.¹ Unfortunately morphine is also metabolised to morphine-3-glucuronide (M3G, 3), a compound which antagonises the analgesic effect of morphine. Since M3G is formed in greater abundance than M6G, there is much interest in using the latter, rather than morphine, as a pain killing drug.²

M6G has been obtained through the selective hydrolytic cleavage of morphine-3,6-diglucuronide (4), using β -glucuronidase as a catalyst,³ but an efficient synthesis involving direct monocoupling between morphine, or codeine, and a glucuronic acid derivative has not yet been fully realised.

Syntheses of M6G and codeine-6-glucuronide (5) have been reported by Yoshimura *et al.*,⁴ but we have been unable to reproduce the methods described and to obtain the final products in a pure form. Similarly, a patent application describes,⁵ as the key step, a reaction between the imidate (6) and 3-acetylmorphine (7). The yield of the 'adduct glycoside' is claimed as 63%, and it is stated that this may be converted into M6G by treatment with 5% NaOH and crystallisation of the product from HOAc. However, although we can routinely prepare the adduct by this route in yields of 10-15%, the M6G obtained from it cannot be purified by crystallisation, as stated, and it is contaminated with NaOAc. The use of other bases presents similar difficulties and, since the glucuronide is highly water soluble, this constitutes a major problem if the method is to be adopted on a large scale.

We have significantly improved the coupling procedure by refluxing (7) (240 mg) in toluene (10 cm³) with the 2- α -bromoglucuronate (8) (600 mg) in the presence of silver carbonate on Celite (1:1)⁶ (2.5 g), which was added in 0.5 g portions over 3h. This gives the 'adduct' (9) (210 mg, 45%), which can be successfully deprotected by either treatment with 0.1M NaOH aq., and then neutralising with HOAc (20mM), or by heating it in H₂O (20mM) with Amberlite IRA410 resin for 10 h., prior to treatment with 0.1M NaOH, and evaporation. In both cases the residue is redissolved in the minimum of 1% MeCN in H₂O and eluted through a Waters Sep-pak C-18 cartridge with this solvent mixture. Initial fractions are rich in inorganic salts and later ones give pure M6G in 85% yield.

This route has also been applied to the syntheses of the glycosides (5) [from codeine (10) and (8)], (11) [from (7) and 2 α -bromo-tetra-*O*-acetylglucose (12)], and (13) [from (10) and (12)], in overall yields close to those for M6G. The weak point in our route is the use of Celite, which appears to promote the decomposition of the 'adducts'. We have tried many other supports and methods but, so far, without improvement, for example, a commonly recommended means of activating a pyranose is *via* the imidate derivative,⁷ however, in our hands a reaction between cyclohexanol and the imidate (14) gives only a 69:31 α : β -selectivity and only a 12% combined yield of the corresponding 'adducts'. Furthermore, no coupling is observed between this activated sugar and codeine, whereas in the reaction of 2-[2,3,4,6-tetra-*O*-benzyl- α , β -glucopyranosyl]oxy 2-pyrimidine (15)⁸ and codeine both α - and β -'adducts' are formed in equal amounts, and in only 35% yield.



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References:

- Osborne, R.; Thompson, P.; Joel, S.; Trew, D.; Patel, N.; Slevin, M; *Br. J. Clin. Pharm.*, 1992, 34, 130.
- Frances, B.; Gout, R.; Monsarrat, B.; Cros, J.; Zajac, J.-M.; *J. Pharm. Exp. Ther.*, 1992, 262, 25.
- Brown, R.T.; Carter, N.E.; Scheinmann, F.; Turner, N.J.; *Tetrahedron Letters*, 1995, 36, 1117.
- Yoshimura, H.; Oguri K.; Tsukamoto, H.; *Chem. Pharm. Bull.*, 1968, 16, 2114.
- Salford Ultrafine Chemicals and Research Ltd. PCT/GB92/01449 (1993).
- Schneider, G.; Sembdner, G.; Schreiber, K.; Phinney, B.O.; *Tetrahedron*, 1989, 45, 1355.
- Schmidt, R.R.; Grundler, G.; *Synthesis*, 1981, 885.
- Vankar, Y.D.; Vankar, P.S.; Behrendt.; Schmidt, R.R.; *Tetrahedron*, 1991, 47, 9985.

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